NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 436

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *t*-BUTYL ALCOHOL

(CAS NO. 75-65-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(DRINKING WATER STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge while supplies last from NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709 (919-541-3419).

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *t*-BUTYL ALCOHOL

(CAS NO. 75-65-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(DRINKING WATER STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

May 1995

NATIONAL INSTITUTES OF HEALTH
NIH LIBRARY
DEC 18 1995
BLDG 10, 10 CENTER DR.
BETHESDA, MD 20892-1150

NTP TR 436

NIH Publication No. 95-3167

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

RC
268.5
T255
no. 436
1995

CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

C.J. Alden, Ph.D.
G.A. Boorman, D.V.M., Ph.D.
D.A. Bridge, B.S.
J.R. Bucher, Ph.D.
J.D. Cirvello, B.S.
M.R. Elwell, D.V.M., Ph.D.
T.J. Goehl, Ph.D.
J.K. Haseman, Ph.D.
A.E. Radovsky, D.V.M., Ph.D.
G.N. Rao, D.V.M., Ph.D.
G.S. Travlos, D.V.M.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

Southern Research Institute

Conducted 13-week and 2-year drinking water studies, evaluated pathology findings

J.D. Prejean, Ph.D., Principal Investigator
D.R. Farnell, Ph.D., D.V.M.
J.E. Heath, D.V.M.
C. Lindamood, III, Ph.D.

Experimental Pathology Laboratories, Inc.

Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
E.T. Gaillard, D.V.M., M.S.
B.F. Hamilton, D.V.M., Ph.D.

Dynamac Corporation

Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

Biotechnical Services, Inc.

Prepared Technical Report

D.D. Lambright, Ph.D., Principal Investigator
S.R. Gunnels M.A.
L.M. Harper, B.S.
M.J. Nicholls, B.S.
K.L. Shaw, B.A.

NTP Pathology Working Group

Evaluated slides, prepared pathology report on rats (30 December 1991)

J.R. Leininger, D.V.M., Ph.D., Chair
Pathology Associates, Inc.
W.W. Carlton, D.V.M., Ph.D.
Purdue University
E.T. Gaillard, D.V.M., M.S.
Experimental Pathology Laboratories, Inc.
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
J.R. Hailey, D.V.M.
National Toxicology Program
M.P. Jokinen, D.V.M.
National Toxicology Program
R.R. Maronpot, D.V.M.
National Toxicology Program
C.C. Shackelford, D.V.M., M.S., Ph.D.
National Toxicology Program

Evaluated slides, prepared pathology report on mice (19 December 1991)

P.K. Hildebrandt, D.V.M., Chair
PATHCO, Inc.
J. Cullen, V.M.D., Ph.D.
North Carolina State University
J.R. Hailey, D.V.M.
National Toxicology Program
B.F. Hamilton, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
M.P. Jokinen, D.V.M.
National Toxicology Program
C.C. Shackelford, D.V.M., M.S., Ph.D.
National Toxicology Program
G. Sykes, V.M.D.
Biosphere Pathology Services, Inc.

Evaluated slides, prepared pathology report on rat kidney step sections (extended evaluations) (3 September 1992)

J.R. Leininger, D.V.M., Ph.D., Chair
Pathology Associates, Inc.
S.L. Eustis, D.V.M., Ph.D.
National Toxicology Program
J.R. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
R.C. Sills, D.V.M., Ph.D.
National Toxicology Program
S. Stefanski, D.V.M., Ph.D.
North Carolina State University

CONTENTS

ABSTRACT 5

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY 10

TECHNICAL REPORTS REVIEW SUBCOMMITTEE 11

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS 12

INTRODUCTION 15

MATERIALS AND METHODS 21

RESULTS 31

DISCUSSION AND CONCLUSIONS 55

REFERENCES 59

APPENDIX A Summary of Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 65

APPENDIX B Summary of Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 111

APPENDIX C Summary of Lesions in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 155

APPENDIX D Summary of Lesions in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 201

APPENDIX E Genetic Toxicology 253

APPENDIX F Organ Weights and Organ-Weight-to-Body-Weight Ratios 265

APPENDIX G Hematology, Clinical Chemistry, and Urinalysis Results 271

APPENDIX H Reproductive Tissue Evaluations and Estrous Cycle Characterization 281

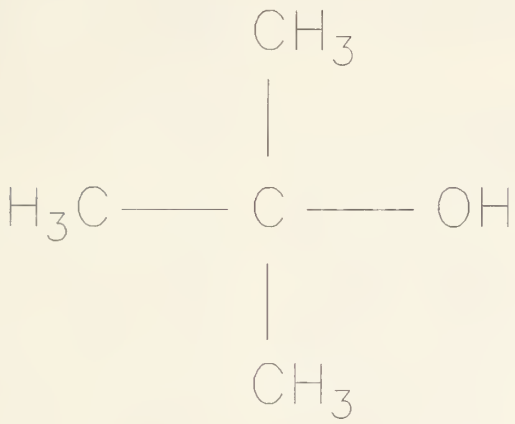
APPENDIX I Chemical Characterization and Dose Formulation Studies 285

APPENDIX J Water and Compound Consumption in the 2-Year Drinking Water Studies 299

APPENDIX K Ingredients, Nutrient Composition, and Contaminant Levels in NIH-07 Rat and Mouse Ration 305

APPENDIX L Sentinel Animal Program 311

ABSTRACT



t-BUTYL ALCOHOL

CAS No. 75-65-0

Chemical Formula: $C_4H_{10}O$ Molecular Weight: 74.12

Synonyms: 2-Methyl-2-propanol, 2-methylpropan-2-ol, TBA, *t*-butanol, tertiary butyl alcohol, *t*-butyl hydroxide, trimethyl carbinol, trimethyl methanol

t-Butyl alcohol is widely used in the manufacture of perfumes and a variety of cosmetics. It is also used as a raw material in the production of isobutylene, which may be used to produce methyl tertiary butyl ether, a common gasoline additive, or to produce butyl elastomers used in the production of automobile tires. Male and female F344/N rats and $B6C3F_1$ mice were given *t*-butyl alcohol (greater than 99% pure) in drinking water for 13 weeks or 2 years. The genetic toxicity of *t*-butyl alcohol was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and by measuring the frequency of micronucleated erythrocytes in mouse peripheral blood.

13-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were given 0, 2.5, 5, 10, 20, or 40 mg/mL *t*-butyl alcohol in drinking water for 13 weeks. All males and six females given 40 mg/mL died during the study. Final mean body weights of 10 and 20 mg/mL males and of 40 mg/mL females were 12%, 17%, or 21% less than those of the corresponding controls, respectively. Serum sorbitol dehydrogenase activities in 10 and 20 mg/mL males were greater than that in the controls after 13 weeks. Serum alanine aminotransferase activity in 40 mg/mL females was greater than that in the controls after 2 weeks and greater in all exposed females after 13 weeks. Urine volumes of 10, 20, and 40 mg/mL males and females decreased, and urine specific gravity values increased. Transitional epithelial hyperplasia and inflammation of the urinary bladder were observed in 20 and 40 mg/mL males and 40 mg/mL females. Absolute and relative liver weights of all exposed groups of females and relative liver weights of 5, 10, and 20 mg/mL males were significantly greater than those of the controls. Absolute and relative kidney weights of all exposed groups of males and females were significantly greater than those of the controls. Incidences of mineralization of the kidney were significantly increased in 10, 20, and 40 mg/mL males. The severity of

nephropathy in 2.5, 5, 10, and 20 mg/mL males was significantly greater than that of the controls as was the accumulation of hyaline droplets in the kidney of 5, 10, and 20 mg/mL males. The incidences of nephropathy in 10, 20, and 40 mg/mL females were significantly greater than that of the controls.

13-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were given 0, 2.5, 5, 10, 20, or 40 mg/mL *t*-butyl alcohol in drinking water for 13 weeks. The deaths of two males and one female in the 40 mg/mL group were attributed to exposure to *t*-butyl alcohol. The final mean body weights of 20 and 40 mg/mL males and 40 mg/mL females were significantly lower than those of the controls. There were no biologically significant differences in hematology parameters of exposed and control groups of mice. Transitional epithelial hyperplasia and inflammation were observed in the urinary bladder of 20 and 40 mg/mL males and 40 mg/mL females.

2-Year Study in Rats

Groups of 60 F344/N rats were given 0, 1.25, 2.5, or 5 mg/mL *t*-butyl alcohol (males) or 0, 2.5, 5, or 10 mg/mL *t*-butyl alcohol (females) in drinking water for 2 years. These correspond to average daily doses of approximately 90, 200, or 420 mg *t*-butyl alcohol/kg body weight for males and approximately 180, 330, or 650 mg *t*-butyl alcohol/kg body weight for females. Ten rats per group were evaluated after 15 months of chemical administration.

Survival, Body Weights, and Water Consumption

Survival rates of 5 mg/mL males and 10 mg/mL females were significantly lower than those of the controls. The final mean body weights of exposed groups of males were 15% to 24% lower than that of the controls, and the final mean body weight of 10 mg/mL females was 21% lower than that of the controls. Water consumption by males increased with dose; water consumption by females decreased with dose.

Hematology and Urinalysis

At the 15-month interim evaluation, there were no significant differences in hematology parameters in males and females, and there were no significant differences in urinalysis parameters in males. Females given 5 or 10 mg/mL had increased urine specific gravities and decreased urine volumes.

Pathology Findings

At the 15-month interim evaluation, relative kidney weights of 2.5 and 5 mg/mL males and absolute and relative kidney weights of 1.25, 2.5, and 5 mg/mL females were significantly greater than those of the controls. At 2 years, the incidence of mineralization in the kidney increased with dose and that of 5 mg/mL males was significantly greater than that of the controls. In the standard evaluation at the end of the study, the incidences of focal renal tubule hyperplasia and of adenoma were increased in exposed males and a carcinoma was observed in one 5 mg/mL male. Renal tubule hyperplasia occurred in one 10 mg/mL female. An extended evaluation of the kidney identified additional male rats with hyperplasia (control, 11/50; 1.25 mg/mL, 13/50; 2.5 mg/mL, 11/50; 5 mg/mL, 19/50) and renal tubule adenoma (7/50, 8/50, 15/50, 10/50); renal tubule carcinomas were identified in two 1.25 mg/mL males and in one 2.5 mg/mL male. Renal tubule adenoma was identified in one 5 mg/mL male from the 15-month extended evaluation. In the standard and extended evaluations combined, there were dose-related increased incidences of hyperplasia and adenoma. The severity of nephropathy and the incidence and severity of transitional cell hyperplasia of the kidney were increased in exposed male and female rats. Linear foci of mineralization were present in the renal papilla of exposed males.

2-Year Study in Mice

Groups of 60 male and 60 female B6C3F$_1$ mice were given 0, 5, 10, or 20 mg/mL *t*-butyl alcohol in drinking water for 2 years. Exposure levels of 5, 10, or 20 mg/mL delivered average daily doses of approximately 540, 1,040, or 2,070 mg *t*-butyl alcohol/kg body weight to males and approximately 510, 1,020, or 2,110 mg/kg to females.

Survival, Body Weights, and Water Consumption

Survival of 20 mg/mL males was significantly lower than that of the controls. The final mean body weights of exposed groups of males were similar to those of the controls. The mean body weights of females given 20 mg/mL were 10% to 15% lower than those of the controls from week 13 to the end of the study. Water consumption by exposed groups of males and females was similar to that by the controls.

Pathology Findings

Incidences of thyroid gland follicular cell hyperplasia were significantly increased in all exposed groups of males and in 10 and 20 mg/mL females. The incidence of follicular cell adenoma or carcinoma (combined) was marginally increased in 10 mg/mL males (0 mg/mL, 1/60; 5 mg/mL, 0/59; 10 mg/mL, 4/59; 20 mg/mL, 2/57). The incidence of follicular cell adenoma was significantly increased in 20 mg/mL females (2/58, 3/60, 2/59, 9/59). The incidences of chronic inflammation and transitional epithelial hyperplasia of the urinary bladder were increased in 20 mg/mL males and to a lesser extent in 20 mg/mL females.

Genetic Toxicology

t-Butyl alcohol was tested for induction of genetic damage *in vitro* and *in vivo*, and all results were negative. *In vitro*, *t*-butyl alcohol was negative in *Salmonella typhimurium* and mouse lymphoma cell mutation tests, and it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. These *in vitro* studies were conducted with and without metabolic activation (S9). *In vivo*, no increase in micronucleated erythrocytes was observed in peripheral blood samples from mice administered *t*-butyl alcohol in drinking water for 13 weeks.

Conclusions

Under the conditions of these 2-year drinking water studies, there was *some evidence of carcinogenic activity** of *t*-butyl alcohol in male F344/N rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was *no evidence of carcinogenic activity* in female F344/N rats receiving 2.5, 5, or 10 mg/mL *t*-butyl alcohol. There was *equivocal evidence of carcinogenic activity* of *t*-butyl alcohol in male $B6C3F_1$ mice based on the marginally increased incidences of follicular cell adenoma or carcinoma (combined) of the thyroid gland. There was *some evidence of carcinogenic activity* of *t*-butyl alcohol in female $B6C3F_1$ mice based on increased incidences of follicular cell adenoma of the thyroid gland.

Exposure to *t*-butyl alcohol was associated with mineralization and renal tubule hyperplasia in male rats, transitional epithelial hyperplasia and increased severity of nephropathy of the kidney in male and female rats, follicular cell hyperplasia of the thyroid gland in male and female mice, and chronic inflammation and hyperplasia of the urinary bladder in male mice and to a lesser extent in female mice.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of *t*-Butyl Alcohol

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 1.25, 2.5, or 5 mg/mL in drinking water [approximately 90, 200, or 420 mg/kg/day]	0, 2.5, 5, or 10 mg/mL in drinking water [approximately 180, 330, or 650 mg/kg/day]	0, 5, 10, or 20 mg/mL in drinking water [approximately 540, 1,040, or 2,070 mg/kg/day]	0, 5, 10, or 20 mg/mL in drinking water [approximately 510, 1,020, or 2,110 mg/kg/day]
Body weights	Exposed groups lower than controls	10 mg/mL group lower than controls	Exposed groups similar to controls	20 mg/mL group lower than controls
2-Year survival rates	10/50, 6/50, 4/50, 1/50	28/50, 24/50, 22/50, 12/50	27/60, 36/60, 34/60, 17/60	36/60, 35/60, 41/60, 42/60
Nonneoplastic effects	Kidney (standard evaluation): mineralization (26/50, 28/50, 35/50, 48/50); transitional epithelial hyperplasia (25/50, 32/50, 36/50, 40/50); severity of nephropathy (3.0, 3.1, 3.1, 3.3); (standard and extended evaluation): renal tubule hyperplasia (14/50, 20/50, 17/50, 25/50)	Kidney: transitional epithelial hyperplasia (0/50, 0/50, 3/50, 17/50); severity of nephropathy (1.6, 1.9, 2.3, 2.9)	Thyroid gland: follicular cell hyperplasia (5/60, 18/59, 15/59, 18/57) Urinary bladder: chronic inflammation (0/59, 3/59, 1/58, 37/59); transitional epithelial hyperplasia (1/59, 3/59, 1/58, 17/59)	Thyroid gland: follicular cell hyperplasia (19/58, 28/60, 33/59, 47/59) Urinary bladder: chronic inflammation (0/59, 0/60, 0/59, 4/57); transitional epithelial hyperplasia (0/59, 0/60, 0/59, 3/57)
Neoplastic effects	Kidney, renal tubule: (standard evaluation): adenoma (1/50, 3/50, 4/50, 2/50); adenoma or carcinoma (combined) (1/50, 3/50, 4/50, 3/50); (standard and extended evaluation): adenoma (8/50, 11/50, 19/50, 13/50); adenoma or carcinoma (combined) (8/50, 13/50, 19/50, 13/50)	None	None	Thyroid gland: follicular cell adenoma (2/58, 3/60, 2/59, 9/59)
Uncertain findings	None	None	Thyroid gland: follicular cell adenoma or carcinoma (combined) (1/60, 0/59, 4/59, 2/57)	None
Level of evidence of carcinogenic activity	Some evidence	No evidence	Equivocal evidence	Some evidence

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of *t*-Butyl Alcohol (continued)

Genetic toxicology	
Salmonella typhimurium gene mutations:	Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9
Mouse lymphoma gene mutations:	Negative with and without S9
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Micronucleated erythrocytes	
Mouse peripheral blood *in vivo*:	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such neoplasms to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant neoplasm incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in neoplasm induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed neoplasm increase;
- concurrent control neoplasm incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on *t*-butyl alcohol on June 21, 1994, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

Arnold L. Brown, M.D., Chair
University of Wisconsin Medical School
Madison, WI

Paul T. Bailey, Ph.D.
Environmental and Health Sciences Laboratory
Mobil Oil Corporation
Princeton, NJ

Meryl H. Karol, Ph.D.
Department of Environmental Occupational Health
University of Pittsburgh
Pittsburgh, PA

Curtis D. Klaassen, Ph.D.
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Claudia S. Miller, M.D.
University of Texas Health Sciences Center
San Antonio, TX

Janardan K. Reddy, M.D.
Department of Pathology
Northwestern University Medical School
Chicago, IL

Irma Russo, M.D., Principal Reviewer
Fox Chase Cancer Center
Philadelphia, PA

Louise Ryan, Ph.D., Principal Reviewer
Division of Biostatistics
Harvard School of Public Health and
Dana-Farber Cancer Institute
Boston, MA

Robert E. Taylor, M.D., Ph.D.
Department of Pharmacology
Howard University College of Medicine
Washington, DC

Matthew J. van Zwieten, D.V.M., Ph.D.
Department of Safety Assessment
Merck Research Laboratories
West Point, PA

Mary Jo Vodicnik, Ph.D.
Lilly MSG Development Center
Belgium

Jerrold Ward, D.V.M., Ph.D., Principal Reviewer
National Cancer Institute
Frederick, MD

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 21, 1994, the draft Technical Report on the toxicology and carcinogenesis studies of *t*-butyl alcohol received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Mr. J.D. Cirvello, NIEHS, introduced the toxicology and carcinogenesis studies of *t*-butyl alcohol by discussing the uses of the chemical and the routes of human exposure to the chemical, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in rats and mice. Because of increased incidences of rare proliferative lesions of the renal tubule in exposed male rats, additional step sections from the kidneys of all control and exposed male rats were prepared and evaluated. The proposed conclusions were *some evidence of carcinogenic activity* of *t*-butyl alcohol in male F344/N rats, *no evidence of carcinogenic activity* of *t*-butyl alcohol in female F344/N rats, *equivocal evidence of carcinogenic activity* of *t*-butyl alcohol in male $B6C3F_1$ mice, and *some evidence of carcinogenic activity* of *t*-butyl alcohol in female $B6C3F_1$ mice.

Dr. Ward, a principal reviewer, disagreed with the proposed conclusion for male rats. He commented that with the standard pathology protocol, there were no significantly increased incidences of renal neoplasms or renal tubule hyperplasia, so no evidence of carcinogenic activity would be the appropriate conclusion. With the step-section technique, the incidence of neoplasms increased significantly in only the 2.5 mg/mL group. Thus, he considered the correct conclusion, based on the extended evaluation in male rats, to be equivocal evidence of carcinogenic activity. Mr. Cirvello responded that, based on the standard evaluation alone, equivocal evidence might be more appropriate. Only one adenoma occurred in controls and none occurred in controls from previous drinking water studies, while there were increased adenomas in all exposure groups in this study as well as a carcinoma in the 5 mg/mL group. Mr. Cirvello asked for discussion on the level of evidence based on the extended evaluation. Dr. J.K. Haseman, NIEHS, recommended that a formal statistical analysis of neoplasm data from the extended evaluation be included in the report to clarify the chemical effect.

Dr. Ward said the pathology protocol should be more detailed and should include the number of step sections in the kidney, an explanation of the severity grading system for hyperplasias, and the number of lesions per section per rat. Dr. A. Radovsky, NIEHS, said the severity of hyperplasia is graded in terms of how closely the lesion resembles an adenoma (i.e., the size of the lesion and the extent of cellular atypia). Sixteen to 17 step sections per rat were taken instead of eight, which was standard in previous studies. She said this information would be added to the report.

Dr. Ryan, the second principal reviewer, questioned the proposed conclusions for male rats and male and female mice. With regard to male rats, she supported equivocal evidence of carcinogenic activity because none of the pairwise tests showed significant increases. Also, the life table trend test was significant but the logistic regression test was probably more relevant. For mice, she proposed no evidence for males and equivocal evidence for females. Although the incidence of thyroid adenomas in 20 mg/mL female mice was significantly greater than that of the controls, she felt this was not a clear exposure-related trend. Dr. Haseman stated that the incidence of combined renal neoplasms in the 2.5 mg/mL male rats was statistically significant by any test and the incidence in the 5 mg/mL group was significant with the addition of the one neoplasm from the interim sacrifice. Other factors supporting some evidence were neoplasm multiplicity at 2.5 mg/mL, increased hyperplasia at 5 mg/mL, and the occurrence of the uncommon carcinomas. With regard to the thyroid follicular cell adenomas in female mice, Dr. Haseman said this is a fairly uncommon neoplasm and the 15% incidence in the 20 mg/mL group was three times the highest incidence in drinking water controls and almost double the highest incidence in feed study controls. In addition, there were supporting increases in hyperplasia at 10 and 20 mg/mL. For male mice, he said that increased hyperplasias and similar but less impressive neoplasm findings than those in females suggested equivocal evidence.

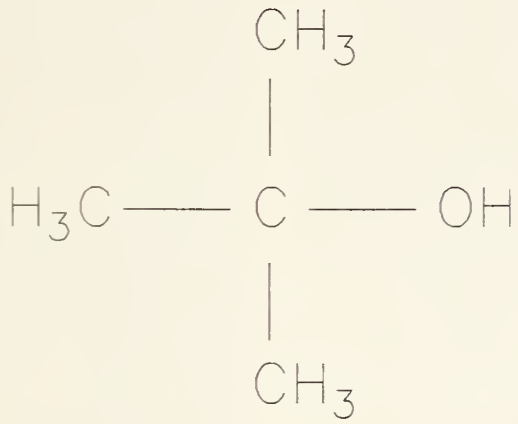
Dr. Ryan asked why the results from 18-day and 13-week inhalation studies were not included in this Technical Report. Mr. Cirvello said that these studies will be reviewed and published separately in a toxicity study report. Dr. Ryan asked why renal tubule hyperplasia was considered rare when this lesion was observed in 12 male control rats in the extended evaluation. Dr. Radovsky responded that these lesions are uncommon in routine single sections of kidney from controls, but increasing the sample size to 16 sections per animal increased observations of this lesion.

Dr. Russo, the third principal reviewer, agreed with the proposed conclusions but had reservations about the proposed conclusion in male rats. She speculated that in this strain of rats, the chemical might be acting more as a promoter. Dr. J.R. Bucher, NIEHS, responded that the study was not designed as a promotion study, and further, the numbers of neoplasms observed in the extended evaluation would argue against a promotion effect. Dr. Russo said the report could benefit from some discussion of the lower susceptibility of female rats to the chemical and of the species-related organ specificity (i.e., kidney in rats versus thyroid in mice). Mr. Cirvello agreed to expand on this in the discussion.

There was more discussion on the merits and timing of extended pathologic evaluations. Dr. Haseman likened it to the difference between a partial evaluation and a definitive evaluation and said he would tend to give higher weight to the more definitive evaluation, which should be closer to the true neoplasms incidence. Dr. Russo urged more uniformity in the number of sections and the way they are taken in extended evaluations. Dr. Bucher commented that the NTP is careful to keep control data from standard histopathologic evaluations separate from data collected under step-section techniques. Dr. van Zwieten said step sections are most useful where an equivocal finding can be resolved through the extended evaluation. Dr. Haseman concurred.

Dr. Ward moved that the Technical Report on *t*-butyl alcohol be accepted with the revisions discussed and with the conclusions as written: *some evidence of carcinogenic activity* of *t*-butyl alcohol in male F344/N rats, *no evidence of carcinogenic activity* of *t*-butyl alcohol in female F344/N rats, *equivocal evidence of carcinogenic activity* of *t*-butyl alcohol in male $B6C3F_1$ mice, and *some evidence of carcinogenic activity* of *t*-butyl alcohol in female $B6C3F_1$ mice. Dr. van Zwieten seconded the motion, which was accepted unanimously with 11 votes.

INTRODUCTION



t-BUTYL ALCOHOL

CAS No. 75-65-0

Chemical Formula: $C_4H_{10}O$ Molecular Weight: 74.12

Synonyms: 2-Methyl-2-propanol, 2-methylpropan-2-ol, TBA, *t*-butanol, tertiary butyl alcohol, *t*-butyl hydroxide, trimethyl carbinol, trimethyl methanol

Chemical and Physical Properties

t-Butyl alcohol is a colorless, volatile liquid with a camphor-like odor. It has a specific gravity of 0.783, is soluble in water, alcohols, esters, ethers, and aromatic and aliphatic hydrocarbons, and forms rhombic crystals at temperatures below 25° C (Hawley, 1981; *Patty's Industrial Hygiene and Toxicology*, 1982).

Use, Production, and Human Exposure

t-Butyl alcohol is used in perfumes, a variety of cosmetic products, and in aerosol sprays used to remove household dust. It is also used as a raw material in the production of isobutylene, which may be used to produce methyl tertiary butyl ether, a common gasoline additive, or to produce butyl elastomers used in the production of automobile tires. *t*-Butyl alcohol has been used as an alcohol denaturant, a dehydration agent, a solvent, and a component in industrial cleaning compounds (Hawley, 1981; Sexton *et al.*, 1986; Cosmetic Ingredient Review, 1989). In 1979, the U.S. Environmental Protection Agency granted a waiver to allow the use of *t*-butyl alcohol as a gasoline octane booster (44 FR 10530); however, this use is not widespread. *t*-Butyl alcohol can be an indirect food additive when used in the preparation and application of coatings for paper and paperboard used as food containers (21 CFR § 176.200). *t*-Butyl alcohol may also be used in surface lubricants employed in the manufacture of metallic articles that contact food (21 CFR § 178.3910). Because of this variety of uses, potential routes of human exposure are topical, inhalation, and ingestion.

t-Butyl alcohol was identified in one of eight samples of mothers' milk obtained from women residing in four different urban areas (Pellizzari *et al.*, 1982). In addition, *t*-butyl alcohol has also been found (but not quantified) in the drinking water in at least one city of five surveyed for volatile organics (Coleman *et al.*, 1976) and in water samples collected before, during,

and after treatment at a New Orleans area municipal water treatment facility (Dowty *et al.*, 1975). The latter report also identified *t*-butyl alcohol in water from a commercial deionizing-charcoal filtering unit.

United States production of *t*-butyl alcohol in 1991 was estimated at 2,990 million pounds (Chemical Economics Handbook, 1993). Based on a survey conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1981 to 1983, an estimated 171,419 workers are potentially exposed to *t*-butyl alcohol in the workplace (NIOSH, 1994). The Occupational Safety and Health Administration has established a permissible exposure limit of 100 ppm or 300 mg/m^3 for *t*-butyl alcohol (29 CFR § 1910.1000).

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

While no published literature was found quantitating the absorption of *t*-butyl alcohol, several studies suggest rapid absorption following oral exposure, inhalation exposure, or intraperitoneal injection. Compared with the primary and secondary alcohols, tertiary alcohols are much more stable biologically and are not readily metabolized. The possible routes of metabolism of tertiary alcohols are direct conjugation of the hydroxyl group with glucuronic acid and oxidation of one or more of the alkyl substituents (Williams, 1959). Early metabolism studies identified glucuronide conjugates of *t*-butyl alcohol in the urine of rabbits (Kamil *et al.*, 1953). Approximately 24% of the single gavage dose of 4 mmol/kg was excreted as glucuronide.

t-Butyl alcohol has been used as an example of a nonmetabolizable alcohol since it cannot form an aldehyde or ketone by dehydrogenation and is not a substrate for alcohol dehydrogenase (Arslanian *et al.*, 1971; Videla *et al.*, 1982). However, *in vitro* studies showed that *t*-butyl alcohol serves as a substrate for rat liver microsomal mixed function oxidase and is demethylated to yield small amounts of formaldehyde and acetone. The reaction pathway appears to involve the interaction of *t*-butyl alcohol with hydroxyl radicals generated from hydrogen peroxide by the microsomes (Cederbaum and Cohen, 1980; Cederbaum *et al.*, 1983). Acetone was also found in small, highly variable amounts in urine and expired air following intraperitoneal injection of 0.75 to 2 g *t*-butyl alcohol/kg in rats indicating that a minimal amount of *t*-butyl alcohol is oxidatively metabolized (Baker *et al.*, 1982). A separate experiment by these investigators using labeled *t*-butyl alcohol suggested that it was not the sole source of acetone but may have stimulated production from other sources. Significant increases in blood levels of acetone have been reported following intraperitoneal doses (1 to 2 g/kg) of *t*-butyl alcohol in rats (Yojay *et al.*, 1982).

t-Butyl alcohol has been shown to protect DNA from the effects of radiation in mouse leukemia cells (Roots and Okada, 1972) or bacteriophage (Lafleur and Loman, 1982), and it is hypothesized that this action is due to the scavenging of hydroxyl radicals by *t*-butyl alcohol.

Liver microsomal enzyme activity was increased threefold in male Sprague-Dawley rats administered *t*-butyl alcohol orally or by intraperitoneal injection 18 hours after the last dose (quantity not specified) (Bechtel and Cornish, 1972). The oral route appeared more effective in eliciting this response, and liver weights were not significantly elevated.

After five days of inhalation exposure to 500 ppm, *t*-butyl alcohol caused a 36% increase in microsomal cytochrome P_{450} in the kidneys of male Sprague-Dawley rats; liver and lung P_{450} were unaffected. After 3 days of inhalation exposure to 2,000 ppm *t*-butyl alcohol, hepatic P_{450} was significantly elevated 28%; kidney P_{450} was not affected, and lung P_{450} was slightly decreased. These results may indicate that a longer duration of exposure is required before induction can be observed in the kidney, whereas concentration may be more important for induction in the liver (Aarstad *et al.*, 1985).

Four male Wistar rats were given a single oral dose of 2.54 g *t*-butyl alcohol/kg (Videla *et al.*, 1982). Six hours after administration, hepatic glutathione concentration was slightly lower, and lipoperoxidation (indicated by diene conjugate formation) was slightly greater than that of controls.

Thurman *et al.* (1980) did not detect oxidation of *t*-butyl alcohol in perfused rat liver based on changes in oxygen uptake or alterations in the levels of reducing cofactors.

t-Butyl alcohol is eliminated slowly from the blood of rats. Following intraperitoneal injection of *t*-butyl

alcohol (2 g/kg) in female Sprague-Dawley rats, the alcohol was essentially not metabolized as indicated by the nearly constant blood levels over a 12-hour period (Thurman and Pathman, 1975). In further investigations (Thurman *et al.*, 1980), female Sprague-Dawley rats were pretreated with *t*-butyl alcohol in saline (5.7% w/v) by gavage every 8 hours for 1 or 2.5 days then were given sufficient *t*-butyl alcohol to elevate their blood concentrations to between 125 and 150 mg%. Eighteen hours were required to eliminate *t*-butyl alcohol completely from the blood of rats pretreated for 2.5 days, and 26 hours were required following pretreatment for 1 day. The rate of elimination of 1.2 g *t*-butyl alcohol/kg body weight was 0.7 mmol/kg per hour and was identical for both pretreated groups. *t*-Butyl alcohol was eliminated from the rat only 6% to 7% as fast as ethanol, which is consistent with the hypothesis that *t*-butyl alcohol is eliminated from the rat very slowly, possibly by glucuronidation. High serum concentrations (9 mM) of *t*-butyl alcohol in Sprague-Dawley rats following 6 hours of inhalation at 2,000 ppm were regarded as possibly reflecting the small extent of metabolism of the compound (Aarstad *et al.*, 1985).

In another study (Beaugé *et al.*, 1981), a dose of 25 mmol/kg was administered by water gavage to female Wistar rats. *t*-Butyl alcohol was eliminated slowly as reflected in a blood concentration of 13.4 mM at 2 hours, 12.57 mM at 5 hours, and 11.35 mM at 20 hours.

Following intraperitoneal doses of 1 g/kg in four rats (Long-Evans and Sprague-Dawley), *t*-butyl alcohol concentration in the blood was measured over 24 hours and the half-life was 9.1 hours (Baker *et al.*, 1982). Approximately 95% of the *t*-butyl alcohol administered in a dose of 1.75 g/kg was excreted unchanged or as a urinary conjugate.

t-Butyl alcohol is also eliminated slowly from the blood of mice. Single intraperitoneal doses of 8.1 mmol/kg administered to nine male Swiss-Webster mice were eliminated from the blood in 8 to 9 hours (McComb and Goldstein, 1979). The same mice then inhaled *t*-butyl alcohol at a concentration sufficient to maintain a mean blood level of 8 mM for 3 days, and *t*-butyl alcohol was not detected in the blood 3 hours after the mice were removed from the vapor chamber. A single intraperitoneal dose of 8.1 mmol *t*-butyl alcohol/kg body weight was then administered (to an unspecified number of mice) 4 hours after the end of the 3-day inhalation period; no *t*-butyl alcohol was detected in the blood 3 hours later. The increased rate of elimination of *t*-butyl alcohol in animals previously exposed may be due to an increased conjugation. These results in mice are in contrast to the findings following pretreatment in rats mentioned earlier (Thurman *et al.*, 1980).

Humans

No information on the absorption, distribution, metabolism, or excretion of *t*-butyl alcohol in humans was found in a search of the available literature.

TOXICITY

Experimental Animals

The oral LD_{50} of *t*-butyl alcohol has been reported as 3.5 g/kg in rats (Schaffarzick and Brown, 1952) and 3.6 g/kg in rabbits (Munch, 1972); 441 mg/kg is the reported LD_{50} for mice by intraperitoneal injection (Maickel and McFadden, 1979). The primary acute effects in animals are signs of alcoholic intoxication.

Tertiary alcohols are metabolized slowly and incompletely, so their toxic effects are especially persistent. Most of the tertiary alcohols are central nervous system depressants. The sedative-intoxicant and withdrawal effects of *t*-butyl alcohol are nearly identical to those of ethanol (LeBlanc and Kalant, 1975; Bellin and Edmonds, 1976; Snell and Harris, 1980; Thurman *et al.*, 1980). *t*-Butyl alcohol is four to five times more potent than ethanol in producing physical dependence in rats and mice (Wallgren, 1960; McComb and Goldstein, 1979; Wood and Laverty, 1979; Thurman *et al.*, 1980). The higher potency of *t*-butyl alcohol in producing dependence is probably related to its slower clearance rate from the body.

A dose of 25 mmol *t*-butyl alcohol/kg body weight administered by water gavage to female Wistar rats resulted in an accumulation of triacylglycerols in the liver accompanied by an early increase in palmitate uptake into triacylglycerols and a delayed enhancement of the free fatty acid level in the blood (Beaugé *et al.*, 1981). There were no significant changes in hepatic and blood phospholipid concentrations at 2, 5, and 20 hours or in the 4-hour lactate/pyruvate ratio.

In a study of five butyl alcohols (method not given), *t*-butyl alcohol was found to have only a slight

inhibitory effect on rat liver mitochondrial respiration and phosphorylation (Thore and Baltscheffsky, 1965). *t*-Butyl alcohol in a 25% aqueous solution was administered intraperitoneally to male Sprague-Dawley rats 18 hours prior to giving carbon tetrachloride (CCl_4) or measuring glutathione (GSH) levels. Serum glutamate-pyruvate transaminase levels were used to evaluate CCl_4-induced hepatotoxicity. *t*-Butyl alcohol was found to potentiate hepatotoxicity due to CCl_4 by a mechanism that did not alter hepatic GSH levels or produce a loss of body weight (Harris and Anders, 1980).

In castrated rats *t*-butyl alcohol was found to be four times as potent as ethanol in lowering plasma levels of luteinizing hormone, which regulates testosterone production (Chapin *et al.*, 1980).

Humans

In some individuals, *t*-butyl alcohol is a mild skin irritant. When the individual components of a sunscreen preparation were patch-tested on a patient with an allergic contact dermatitis, *t*-butyl alcohol was determined to be the cause (Edwards and Edwards, 1982). No other adverse effects of *t*-butyl alcohol on humans were found in the literature.

Reproductive and Developmental Toxicity

Experimental Animals

The effects of prenatal administration of *t*-butyl alcohol and ethanol on postnatal development were compared in Swiss-Webster mice (Daniel and Evans, 1982). A liquid diet containing either 0.5%, 0.75%, or 1.0% *t*-butyl alcohol or 3.6% ethanol was fed to pregnant mice from day 6 to day 20 of gestation. The *t*-butyl alcohol diet resulted in a dose-related reduction in number of litters, litter size, and birth weights, and an increase in the number of stillborn. Testing of pups indicated that *t*-butyl alcohol was approximately five times more potent than ethanol in producing a developmental delay in postnatal physiological and psychomotor performance.

t-Butyl alcohol and ethanol were compared for their ability to induce microcephaly in the neonatal rat (Grant and Samson, 1982). Neonatal Long-Evans rats were reared using an artificial feeding technique (cannulation) from postnatal day 4 through day 18. On postnatal days 4 through 7, *t*-butyl alcohol or ethanol was administered in the milk formula. Mean daily doses of *t*-butyl alcohol were 0.60, 1.44, 2.16, and 2.69 g/kg body weight. The doses were calculated to be of equal anesthetic value to the ethanol doses by using membrane-to-buffer partition coefficients. Following the 4-day alcohol exposure, all animals were given a plain milk formula until day 18. A similar degree of microcephaly was present in both alcohol treated groups but not in controls. The general impairment of brain growth could be due to the membrane solubilizing properties of the alcohols.

In vitro studies showed that ethanol reduced the fertilizing capacity of mouse spermatozoa at concentrations commonly observed after ethanol ingestion by man and experimental animals (100 to 44 mg%). At similar concentrations, *t*-butyl alcohol had no effect on fertilization (Anderson *et al.*, 1982).

Pregnant CBA/J and C57ABL/6J mice were given *t*-butyl alcohol (10.5 mmol/kg) or an equivalent volume of tap water by gavage every 12 hours from day 6 through day 18 of gestation (Faulkner *et al.*, 1989). On day 18, there were significantly more resorptions per litter in the mice receiving *t*-butyl alcohol but no interstrain difference. Blood concentration profiles in the C57ABL/6J mice showed that the treatment regimen produced *t*-butyl alcohol blood levels equivalent to teratogenic ethanol treatment. However, body weights of the survivors were not affected, and significant abnormalities were not found in either strain of animals receiving *t*-butyl alcohol.

In a teratology assessment of *t*-butyl alcohol, 1-butanol, and 2-butanol, pregnant Sprague-Dawley rats were exposed by inhalation to 0, 2,000, 3,500, or 5,000 ppm *t*-butyl alcohol for 7 hours per day on gestation days 1 through 19 (Nelson *et al.*, 1989). Dams were sacrificed on day 20, and fetuses were examined for skeletal abnormalities or visceral defects. Dose-related reductions in fetal weight were observed for each of the butanol isomers; however, concentrations 50 times the current permissible exposure limit (100 ppm) did not produce teratogenicity.

In further investigations by Nelson *et al.* (1991), pregnant Sprague-Dawley rats were exposed to 2,000 or 4,000 ppm *t*-butyl alcohol by inhalation for 7 hours per day on gestation days 1 through 19; males were similarly exposed for 6 weeks and mated to unexposed females. The high concentration of *t*-butyl alcohol was maternally toxic, reducing maternal feed intake and weight gain. However, the few behavioral or neurochemical effects noted in the offspring on

tests conducted through 90 days of age were not considered biologically significant.

Humans

No information on the reproductive and developmental toxicity of *t*-butyl alcohol in humans was found in a search of the available literature.

Carcinogenicity

Experimental Animals

No studies of the carcinogenicity of *t*-butyl alcohol were found; however, an experiment was conducted to test the ability of *t*-butyl alcohol to act as a promoter. Hair was clipped from the backs of female ddN mice (number not specified) and 0.05 mg of 4-nitroquinoline-1-oxide in benzene was applied to the area three times per week for a total of 20 applications. This was followed by applications of 16.6% *t*-butyl alcohol (actual dose not specified) in benzene six times per week for a total of 270 applications. About 150 days after the start of the experiment and after about 100 applications of *t*-butyl alcohol, one tumor was observed which was reported to have rapidly developed into squamous cell carcinoma (Hoshino *et al.*, 1970).

Humans

No information on the carcinogenicity of *t*-butyl alcohol in humans was found in a search of the available literature.

Genetic Toxicity

The published genotoxicity data for *t*-butyl alcohol are from two studies, both of which are presented in Appendix E of this report. Results showed no induction of mutations by *t*-butyl alcohol in any of four strains of *Salmonella typhimurium* (Zeiger *et al.*, 1987) or in L5178Y mouse lymphoma cells (McGregor *et al.*, 1988). Both studies were performed with and without S9.

Study Rationale

The National Cancer Institute nominated *t*-butyl alcohol for study as a result of a review of chemicals found in drinking water. It was selected for study because of its large annual production and potential for human exposure. Because of concerns regarding possible exposure to *t*-butyl alcohol from gasoline fumes, 18-day and 13-week inhalation studies were also conducted in rats and mice. Since these studies did not show additional toxicity, a 2-year inhalation study was not performed. The results of the prechronic inhalation studies will be reported separately. This report presents the results of 13-week and 2-year drinking water studies in F344/N rats and B6C3F$_1$ mice. In addition, the genetic toxicity of *t*-butyl alcohol was assessed in *Salmonella typhimurium* and L5178Y mouse lymphoma cell mutation studies, in cultured Chinese hamster ovary cytogenetic studies, and in the mouse peripheral blood micronucleus test.

MATERIALS AND METHODS

Procurement and Characterization of *t*-Butyl Alcohol

t-Butyl alcohol was obtained from FBC Chemical Corporation (Lancaster, NY) in one lot (F112784), which was used throughout the 13-week and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO; Appendix I). Reports on analyses performed in support of the *t*-butyl alcohol studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a clear colorless liquid, was identified as *t*-butyl alcohol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Purity was determined by elemental analyses, Karl Fischer water analysis, and gas chromatography. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for *t*-butyl alcohol. Karl Fischer water analysis indicated 0.026% ± 0.001% water. Gas chromatography using two systems indicated one major peak and one impurity with a peak area greater than or equal to 0.1% relative to the major peak. The overall purity was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using gas chromatography. These studies indicated that *t*-butyl alcohol was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature protected from light in amber glass bottles with Teflon-lined lids.

Stability was monitored during the 13-week and 2-year studies using gas chromatography. No degradation of the bulk chemical was detected.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared by mixing *t*-butyl alcohol with deionized water (Table I1). Stability studies of the 0.5 mg/mL dose formulations were performed by the analytical chemistry laboratory using gas chromatography. The stability of the dose formulations was confirmed for at least 3 weeks at room temperature when stored in the dark and for at least 3 days at room temperature under normal room light.

Periodic analyses of the dose formulations of *t*-butyl alcohol were conducted at the study laboratory and analytical chemistry laboratory using gas chromatography. For the 13-week drinking water studies, the formulations were analyzed at the beginning, middle, and end of the studies (Table I2). During the 2-year studies, the formulations were analyzed approximately every 8 weeks (Table I3). All dose formulations analyzed were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I4).

13-Week Studies

The 13-week drinking water studies were conducted to evaluate the cumulative toxic effects of repeated exposure to *t*-butyl alcohol and to determine the appropriate doses to be used in the 2-year studies. Male and female F344/N rats and $B6C3F_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 12 or 13 days. The animals were approximately 6 weeks old on the first day of the studies. Before initiation of the studies, five male and five female rats and mice were randomly selected for

parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female control rats and on five male and five female sentinel mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats and mice were given concentrations of 0, 2.5, 5, 10, 20, or 40 mg/mL *t*-butyl alcohol in deionized water for 92 to 94 (rats) and 94 to 95 (mice) consecutive days. The doses used in these studies were based on findings in unpublished 14-day and 13-week studies previously conducted for the NTP. Control animals were given deionized water. Feed was available *ad libitum*, except during urine collection (rats only); deionized water, plain or dosed, was available *ad libitum* throughout the study. After quarantine, rats and mice were housed in individual cages suspended on stainless steel racks, which were rotated every 2 weeks. Body weights and clinical findings were recorded weekly and at the end of the studies for all animals. Water consumption was recorded weekly by cage. Details of the study design and animal maintenance are summarized in Table 1.

Twice during the 13-week drinking water study in rats (days 10-11 and prior to terminal sacrifice), urine was collected from all dose groups. The rats were fasted during this time; water (plain or dosed) was available *ad libitum*. Urinalysis parameters measured are listed in Table 1.

Blood samples were collected from the retroorbital sinus of all rats at an interim period (days 15-16) and at the end of the studies for hematology and clinical chemistry analyses. At the end of the studies, blood samples were collected from the retroorbital sinus of all mice for hematology analysis. Automated hematology determinations were performed with an Ortho ELT-8 Laser Hematology Counter (Ortho Instruments, Westwood, MA). Automated clinical chemistry determinations were performed with a CentrifiChem System 500 Analyzer. The hematology and clinical chemistry parameters measured are listed in Table 1.

At the end of the studies, samples were collected for sperm morphology and vaginal cytology evaluations from all rats and mice in all exposure groups. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP General Statement of Work (April, 1984). For 7 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (*i.e.*, diestrus, proestrus, estrus, and metestrus). All male animals used in this special study were evaluated for sperm morphology, count, and motility. The right testis and right epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each right cauda epididymis was placed in buffered saline solution. Cauda were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed for all animals. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on male and female rats from the 0, 20, and 40 mg/mL groups, on control and 40 mg/mL male and female mice, on 20 mg/mL male mice, and on one 2.5 mg/mL female mouse which died early. The kidneys and gross lesions of all exposed groups of male and female rats and the liver and urinary bladder of 10 mg/mL male rats were examined. Selected organs (liver, urinary bladder, and mesentery of male and female mice, kidney of male mice, and uterus, skin, and thymus of female mice) and gross lesions of 10 mg/mL males and of 20 mg/mL females

were also examined to determine the no-effect level of *t*-butyl alcohol. Table 1 lists the tissues and organs examined.

An additional review of kidney sections from male rats in this study was performed using Mallory Heidenhain and Lee's methylene blue basic fuschin stains to characterize and quantitate changes in accumulation of hyaline droplets and associated crystalline structures.

2-Year Studies

Study Design

Groups of 60 male rats were given 0, 1.25, 2.5, or 5 mg/mL *t*-butyl alcohol; groups of 60 female rats were given 0, 2.5, 5, or 10 mg/mL *t*-butyl alcohol; and groups of 60 male and female mice were given 0, 5, 10, or 20 mg/mL *t*-butyl alcohol in deionized water for 103 weeks. Deionized water was provided to the control groups throughout the studies.

Several days prior to the 15-month interim evaluation, urine samples were collected from previously designated rats. The rats were fasted during this time; deionized water (plain or dosed) was available *ad libitum*. Urinalysis parameters measured are listed in Table 1.

Also at the 15-month interim sacrifice, previously designated rats were anesthetized with carbon dioxide, and blood samples were taken from the retro-orbital sinus for hematology analyses. Automated determinations were performed with an Ortho ELT-8 Laser Hematology Counter (Ortho Instruments, Westwood, MA). The hematology parameters measured are listed in Table 1. Blood samples were also collected from the sentinel animals at approximately 6-month intervals and from the control groups at terminal sacrifice for serologic analyses.

Source and Specification of Animals

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 2-year studies. On receipt, the rats and mice were approximately 5 weeks old. Rats and mice were quarantined for 13 days before the beginning of the studies. Five male and five female rats and mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. The animals were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Rats and mice were housed individually in solid-bottom, polycarbonate cages lined with hardwood-chip bedding. Feed was available *ad libitum*, except during urine collection (rats only) at the 15-month interim. Deionized water, plain or dosed, was available *ad libitum*. Water consumption was measured per animal every two weeks. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

All animals were observed twice daily throughout the study. Clinical findings and body weights were recorded weekly for the first 13 weeks, then every 4 weeks, and at the 15-month interim evaluation and terminal sacrifice. An interim evaluation was conducted at 15 months on rats in all exposure groups for hematology and urinalysis evaluations.

A complete necropsy and microscopic examination were performed on all rats and mice. At the 15-month interim evaluation, the brain, right kidney, and liver of rats were weighed. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, quality assessment pathologists reviewed the kidney,

duodenum, forestomach, and glandular stomach of male and female rats and the thyroid gland, urinary bladder, and liver of male and female mice.

Step sections were made from the residual kidney wet tissue from treated male rats in the 2-year studies because microscopic examination of the original kidney sections showed increased proliferative lesions of the renal tubules. Sectioning was done in 1 mm steps throughout the kidney wet tissue that remained after the standard sections had been taken. (Sections for the standard evaluation were prepared from slices approximately 5 mm thick from the mid-longitudinal plane of the left kidney and the mid-transverse plane of the right kidney.) In this study, wet tissues from both sides of the samples used for the standard sections were available. An average of eight additional step sections per kidney were made. The average number of sections per animal was 16 in the 0, 1.25, and 2.5 mg/mL groups and 17 in the 5 mg/mL group. Criteria for evaluation of proliferative lesions for the kidney step sections were the same as those used in the standard evaluation. Severity grades of renal tubule epithelial hyperplasia were based on the size, complexity and disorganization of the lesion; higher severity grades reflected more progression toward adenoma. The severity grade of the most advanced lesion was given when more than one hyperplastic focus occurred in an animal.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues and any other tissues for which a disagreement in diagnosis between the laboratory and quality assessment pathologists existed. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this

approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if the fit of the model was not significantly enhanced. The neoplasm incidences of exposed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Clinical pathology, spermatid, and spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Because the vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with normality assumptions. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across dose levels.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file

at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of *t*-butyl alcohol was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and mutations in L5178Y mouse lymphoma cells, and by measuring the frequency of micronucleated erythrocytes in peripheral blood of male and female mice. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of *t*-butyl alcohol are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of *t*-Butyl Alcohol

13-Week Studies	2-Year Studies
Study Laboratory	
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)
Strain and Species	
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source	
Frederick Cancer Research Facility (Frederick, MD)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies	
Rats: 12 days Mice: 13 days	13 days
Average Age When Studies Began	
6 weeks	7 weeks
Date of First Dose	
Rats: 2 December 1985 Mice: 10 December 1985	Rats: 12 November 1986 Mice: 19 November 1986
Duration of Dosing	
Rats: 92-94 days Mice: 94-95 days	103 weeks
Date of Last Dose	
Rats: 3-5 March 1986 Mice: 13-14 March 1986	Rats: 1 November 1988 Mice: 8 November 1988
Necropsy Dates	
Rats: 3-5 March 1986 Mice: 13-15 March 1986	Rats: 15-month interim – 10 February (males) or 11 February 1988 (females) Terminal – 9-11 November 1988 Mice: 15-22 November 1988
Average Age at Necropsy	
19 weeks	110 weeks
Size of Study Groups	
10 males and 10 females	60 males and 60 females
Method of Distribution	
Animals randomized from weight classes into cage groups using a random numbers table; cages randomized into test groups using a random numbers table	Same as 13-week studies
Animals per Cage	
1 per cage compartment	1
Method of Animal Identification	
Toe clip	Toe clip

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of *t*-Butyl Alcohol
(continued)

13-Week Studies	2-Year Studies
Diet	
NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during urine collection (rats); changed weekly	Same as 13-week studies
Water Distribution	
City water filtered and deionized, *ad libitum*	Same as 13-week studies
Cages	
Solid-bottom polycarbonate cages (Lab Products, Inc., Maywood, NJ), changed weekly, rotated every 2 weeks	Same as 13-week studies
Bedding	
Beta-Chips® heat-treated hardwood chips (Northeastern Products, Inc., Warrensburg, NY), changed weekly	Same as 13-week studies, also used Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ)
Racks	
Stainless steel racks (Lab Products, Inc., Maywood, NJ), changed every 2 weeks	Same as 13-week studies
Animal Room Environment	
Temperature: 18-24° C (rats), 12-30° C (mice) Relative humidity: 32% to 58% (rats), 31% to 56% (mice) Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour	Temperature: 19-31° C (rats), 13-28° C (mice) Relative humidity: 52% to 59% (rats), 50% to 56% (mice) Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour
Doses	
0, 2.5, 5, 10, 20, or 40 mg/mL in deionized water, available *ad libitum*	Rats: 0, 1.25, 2.5, or 5 mg/mL (males), or 0, 2.5, 5, or 10 mg/mL (females) in deionized water, available *ad libitum* Mice: 0, 5, 10, or 20 mg/mL; in deionized water, available *ad libitum*
Type and Frequency of Observation	
Observed twice daily; animals were weighed initially, weekly, and at the end of the studies. Clinical observations were recorded weekly. Water consumption was recorded weekly.	Observed twice daily; animals were weighed and clinical observations were recorded initially, weekly for 13 weeks, every 4 weeks thereafter, and at interim evaluation and at terminal sacrifice. Water consumption was recorded every 4 weeks.
Method of Sacrifice	
Carbon dioxide	Carbon dioxide
Necropsy	
Necropsy performed on all animals. Organs weighed were the brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals. Organs weighed at the 15-month interim evaluation (rats only) were the brain, right kidney, and liver.

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of *t*-Butyl Alcohol
(continued)

13-Week Studies	2-Year Studies
Clinical Pathology	
Blood was collected from all rats at an interim period (days 15-16) and from all animals at terminal sacrifice from the retroorbital sinus. Urine was collected from rats on days 10-11 and prior to terminal sacrifice. ***Hematology:*** hematocrit, hemoglobin, erythrocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelets, reticulocytes, leukocytes, segmented neutrophils, bands (mice only), lymphocytes, atypical lymphocytes (rats only), monocytes, eosinophils, and nucleated erythrocytes (rats only). ***Clinical chemistry (rats only):*** alkaline phosphatase, alanine aminotransferase, sorbitol dehydrogenase, γ-glutamyltransferase, and bile salts. ***Urinalysis (rats only):*** volume, specific gravity, and pH.	Blood was collected from rats at the 15-month interim evaluation. ***Hematology:*** hematocrit, hemoglobin, erythrocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelets, leukocytes, segmented neutrophils, lymphocytes, atypical lymphocytes, monocytes, and eosinophils. ***Urinalysis:*** Samples were taken several days prior to the 15-month interim evaluation in rats and evaluated for volume, pH, appearance, microscopic sediment, and specific gravity.
Histopathology	
Complete histopathology was performed on all rats in the 0, 20, and 40 mg/mL groups and on all mice in the 0 and 40 mg/mL groups, on 20 mg/mL male mice, and on one 2.5 mg/mL female mouse. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone (marrow, femur, sternum), brain (three sections), clitoral gland (rats), esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph node (mandibular and mesenteric), mammary gland, nose (three sections), ovary, pancreas, pituitary gland, parathyroid gland, preputial gland (rats), prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular stomach), testis (epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus. The kidney in remaining rats and the liver and urinary bladder of 10 mg/mL male rats were examined. The liver, mesentary, and urinary bladder in remaining mice, the kidney in remaining male mice, and the skin, thymus, and uterus in remaining female mice were examined to the no effect level.	Complete histopathology was performed on all animals. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone (marrow, femur, and sternum), brain (three sections), clitoral gland (rats), esophagus, gallbladder (mice), heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidneys, liver, lung, mammary gland, mandibular and mesenteric lymph nodes, nose (three sections), ovary, pancreas, parathyroid gland, pituitary, preputial gland (rats), prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular stomach), testis (epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.
Sperm Morphology and Vaginal Cytology Evaluations	
At terminal sacrifice sperm samples were collected from all male animals for sperm morphology evaluations. The parameters evaluated included: sperm count, morphology, and motility. The right cauda, right epididymis, and right testis were weighed. Vaginal samples were collected for up to 7 consecutive days prior to the end of studies from all female animals for vaginal cytology evaluations. The parameters evaluated included: relative frequency of estrous stages and estrous cycle length.	None

RESULTS

Rats

13-Week Study

All males and six females given 40 mg/mL died before the end of the study (Table 2). The final mean body weights of 10 and 20 mg/mL males were 12% and 17% lower than that of the controls, respectively. The final mean body weight of 40 mg/mL females was 21% lower than that of the controls. Mean body weight gains of 10 and 20 mg/mL males and of 40 mg/mL females were also significantly lower than those of the controls.

During the first week of the study, water consumption by males and females given 10, 20, or 40 mg/mL was less than that by the controls; water consumption by females given 10, 20 or 40 mg/mL was also less during the last week of the study. Water consumption by males given 2.5 or 5 mg/mL was greater than that by the controls during the last week of the study.

Table 2
Survival, Mean Body Weights, and Water Consumption of Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol

Dose (mg/mL)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Water Consumption[c] Week 1	Week 13
Male							
0	10/10	117 ± 2	355 ± 7	238 ± 5		18	21
2.5	10/10	115 ± 2	341 ± 4	227 ± 4	96	17	25
5	10/10	113 ± 2	339 ± 5*	225 ± 4*	95	18	26
10	10/10	115 ± 2	313 ± 5**	198 ± 5**	88	14	22
20	10/10	114 ± 2	294 ± 4**	180 ± 4**	83	12	19
40	0/10[d]	111 ± 4	–	–	–	10	–
Female							
0	10/10	91 ± 1	179 ± 4	88 ± 2		15	15
2.5	10/10	91 ± 2	183 ± 3	91 ± 4	102	16	15
5	10/10	92 ± 2	180 ± 3	88 ± 3	100	16	16
10	10/10	91 ± 1	181 ± 3	90 ± 2	101	11	12
20	10/10	93 ± 2	176 ± 2	83 ± 1	98	10	11
40	4/10[e]	91 ± 1	141 ± 13**	49 ± 15**	79	10	11

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving at 13 weeks/number initially in group. No data were calculated for groups with 100% mortality.
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Water consumption is expressed as grams of water consumed per animal per day.
[d] Week of death: 4, 5, 5, 6, 7, 8, 8, 8, 12, 12
[e] Week of death: 2, 8, 8, 10, 12, 12

Exposure levels of 2.5, 5, 10, 20, or 40 mg/mL delivered average daily doses of approximately 230, 490, 840, 1,520, or 3,610 mg *t*-butyl alcohol/kg body weight to males and approximately 290, 590, 850, 1,560, or 3,620 mg/kg to females.

Dose-related clinical findings in exposed rats included ataxia, hypoactivity, and emaciation for males, and ataxia, hyperactivity, and emaciation for females.

Hemoglobin concentrations and erythrocyte counts were mildly decreased in 10 and 20 mg/mL males at week 13 indicating a mild anemia (Table G1). Additionally, the urine specific gravity was increased and urine volume decreased in 10, 20, and 40 mg/mL male and female rats, findings compatible with reduced water intake. This would have resulted in hemoconcentration of dehydration and could have interfered with the ability to detect anemia. Serum alkaline phosphatase activity was decreased at day 15 in 20 and 40 mg/mL males and 5 and 20 mg/mL females, suggesting decreased feed consumption. Minimal increases occurred in alanine aminotransferase activity in 40 mg/mL female rats at day 15 and all exposed groups of females at week 13. Sorbitol dehydrogenase activity was increased minimally in 10 and 20 mg/mL males at week 13. Both of these increases were minimal and not consistent between males and females, but the distribution was dose related, suggesting a possible mild liver effect.

The absolute and relative kidney weights of all exposed groups of males and females were significantly greater than those of the controls (Table F1). The absolute and relative liver weights of all exposed groups of females and relative liver weights of 5, 10, and 20 mg/mL males were significantly greater than those of the controls. Other differences in organ weights were secondary to body weight changes.

The urinary bladder contained grossly visible calculi, microscopic inflammation of the lamina propria, and hyperplasia of the transitional epithelium in 20 and 40 mg/mL males. Inflammation and hyperplasia in the absence of grossly visible calculi occurred in the urinary bladder of 40 mg/mL females (Table 3). Chronic inflammation of the urinary bladder consisted of increased numbers of macrophages, lymphocytes, and plasma cells in the lamina propria. The hyperplasia of the transitional epithelium of the urinary bladder varied in severity and morphology. In some rats, hyperplasia was a diffuse lesion that consisted of an increased number of layers of mucosal epithelium (e.g., from the normal two to three layer thickness to five to seven layers). Other hyperplastic lesions were papillary, consisting of simple unbranched fibrovascular cores covered with thickened layers or branches of transitional epithelium projecting into the lumen of the urinary bladder.

The severity of nephropathy was significantly greater than that of the controls in 2.5, 5, 10, and 20 mg/mL males. There was a dose-related increase in the incidence of nephropathy in females, and the incidences in 10, 20, and 40 mg/mL females were significantly greater than that of the controls; however, the severities were similar to that of the controls (Table 3). Nephropathy is present as a spontaneous background lesion in F344/N rats and in a 13-week study typically consists of scattered renal tubules lined by basophilic regenerating tubule epithelium. The treatment-related exacerbation of the severity of nephropathy in this study was characterized by an increase in the number and size of foci of regeneration; occasionally a dilated tubule with a protein cast was present in rats with a moderate severity of nephropathy. Mallory Heidenhain and Lee's methylene blue basic fuschin stains demonstrated an increased incidence of hyaline droplets and angular crystalline structures associated with the hyaline droplets within renal tubule epithelium and tubule lumina. Increased hyaline droplet accumulation was minimal in rats given 2.5 mg/mL. This lesion was more prominent but similar in severity in the 5, 10, and 20 mg/mL groups. Hyaline droplets were not present in the 40 mg/mL group in which all rats died prior to the end of the study.

The incidence of mineralization of the kidney was significantly increased in male rats given 10, 20, or 40 mg/mL and the lesion was present in all exposed groups of females (Table 3). Mineralization consisted of focal mineral deposits primarily at the cortico-medullary junction, consistent with the spontaneously occurring degenerative lesion that is usually more prominent in untreated females than in untreated males.

No significant differences in sperm morphology or motility or in estrous cycle length or percentage of time spent in the various estrous stages occurred during the 13-week study (Table H1).

TABLE 3
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol

Dose	0 mg/mL		2.5 mg/mL		5 mg/mL		10 mg/mL		20 mg/mL		40 mg/mL	
Male												
Kidney[a]	10		10		10		10		10		10	
Mineralization[b]	0		0		2	(1.5)[d]	8**	(1.4)	4*	(1.0)	4*	(1.0)
Nephropathy	7	(1.0)	10	(1.6)*	10	(2.6)**	10	(2.7)**	10	(2.6)**	7	(1.1)
Hyaline Droplet Accumulation[c]	0		+		++		++		++		0	
Urinary bladder	10		–[e]		–		10		10		10	
Inflammation, Chronic	0		–		–		0		1	(3.0)	2	(1.5)
Transitional Epithelial Hyperplasia	0		–		–		0		1	(3.0)	7**	(2.9)
Calculi (gross observation only)	0		0		0		0		1		6	
Female												
Kidney	10		10		10		10		10		10	
Mineralization	10	(1.7)	10	(2.0)	10	(2.0)	10	(2.0)	10	(2.0)	6	(1.2)
Nephropathy	2	(1.0)	3	(1.0)	5	(1.0)	7*	(1.0)	8*	(1.0)	7*	(1.0)
Urinary bladder	10		–		–		–		10		10	
Inflammation, Chronic	0		–		–		–		0		1	(2.0)[f]
Transitional Epithelial Hyperplasia	0		–		–		–		0		3	(2.0)

* Significantly different (P≤0.05) from the control group by the Fisher exact test (incidences) or the Mann-Whitney U test (severity grades)
** P≤0.01
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] ++ or + indicates an increased accumulation relative to controls
[d] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate. Note: Grades reflect slight differences in nephropathy (foci of regeneration) between groups within this 13-week study and are not comparable to the changes indicated by similar severity grades for nephropathy in the 2-year study.
[e] Organ not examined at this dose level.
[f] n=6

Dose Selection Rationale

Based on the lower mean body weight gain and urine volume observed in 10 mg/mL males in the 13-week study, the high dose selected for the 2-year drinking water study in male rats was 5 mg/mL. No effect on mean body weight gain was observed in 10 mg/mL female rats in the 13-week study, and the reduced urine volume observed in this group was not considered to affect survival adversely. Thus, 10 mg/mL was selected as the high dose for females in the 2-year drinking water study. The slight increase in renal tubule epithelial regeneration (nephropathy) in 5 mg/mL male rats and 10 mg/mL female rats was not considered to be severe enough to affect survival in a 2-year study.

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 4 and in the Kaplan-Meier survival curves (Figure 1). The survival rates of 5 mg/mL males and 10 mg/mL females were significantly lower than those of the controls.

Body Weights, Water and Compound Consumption, and Clinical Findings

At approximately week 20, mean body weight gain of the 5 mg/mL males was lower than that of the controls. The final mean body weight of this group was 24% less than that of the controls (Figure 2 and Table 5). Mean body weights of males in the 1.25 and 2.5 mg/mL groups were similar to that of the controls through about week 65 and then decreased for the remainder of the study. The mean body weight of 10 mg/mL females was similar to that of the controls through about week 29, then the mean body weight gain of this group was lower than that of the controls. The final mean body weight of 10 mg/mL females was 21% lower than that of the controls (Figure 2 and Table 6). Mean body weights of other exposed groups of females were similar to that of the control group throughout the study.

During the second year of the study, a dose-related increase in water consumption occurred in males; exposed females demonstrated a dose-related decrease in water consumption (Tables J1 and J2). Exposure levels of 1.25, 2.5, or 5 mg/mL delivered average daily doses of approximately 90, 200, or 420 mg *t*-butyl alcohol/kg body weight to males. Exposure levels of 2.5, 5, or 10 mg/mL delivered average daily doses of approximately 180, 330, or 650 mg *t*-butyl alcohol/kg body weight to females.

Behavior and general health and appearance of exposed male and female rats were similar to those of the controls, with the exception of an increased incidence of hyperactivity in 10 mg/mL females.

Hematology and Urinalysis

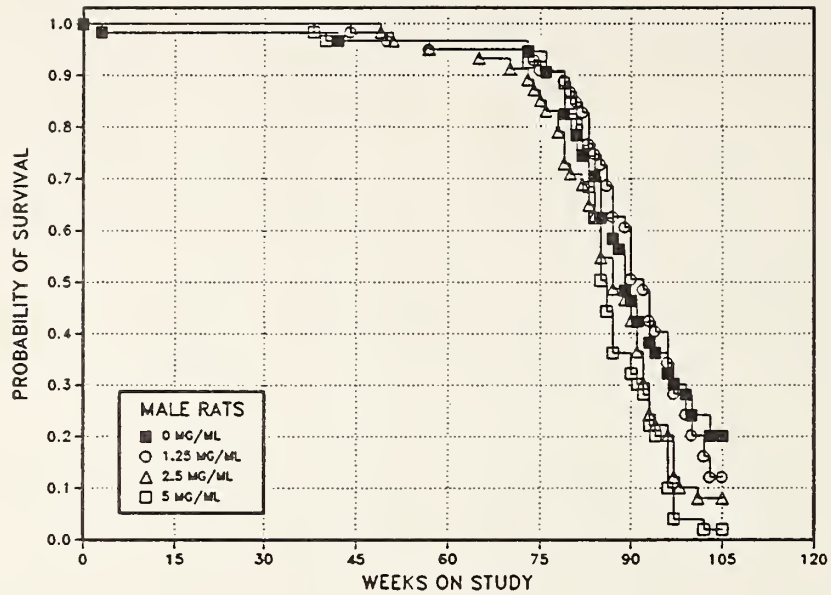
A few minor, sporadic changes that were not considered related to exposure to *t*-butyl alcohol occurred in the hematology and urinalysis parameters (Table G2). Females given 5 or 10 mg/mL demonstrated increased urine specific gravities and decreased urine volumes consistent with their decreased water intake.

TABLE 4
Survival of Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Moribund	31	35	41	46
Natural deaths	9	9	5	3
Animals surviving to study termination	10	6	4	1
Percent probability of survival at end of study[b]	20	12	8	2
Mean survival (days)[c]	618	625	598	596
Survival analysis[d]	P=0.001	P=0.853	P=0.091	P=0.010

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Moribund	15	18	21	35
Natural deaths	7	8	7	3
Animals surviving to study termination	28	24	22	12
Percent probability of survival at end of study	56	48	44	24
Mean survival (days)	669	649	642	643
Survival analysis	P=0.004	P=0.475	P=0.334	P=0.006

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice.
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns.



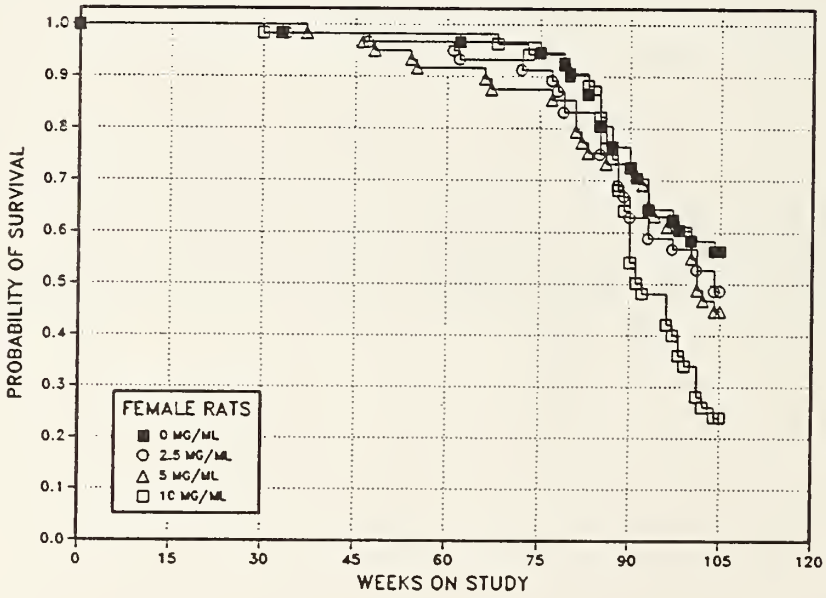
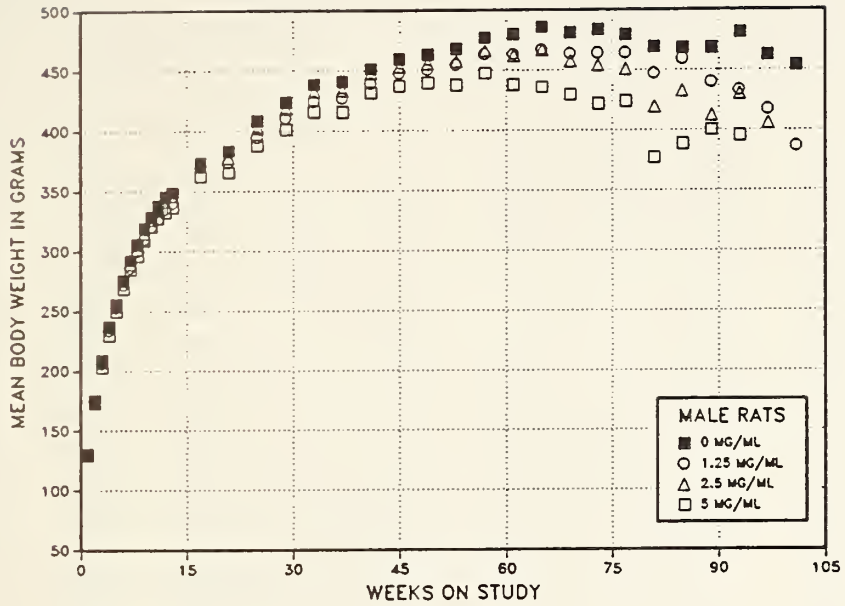


FIGURE 1
Kaplan-Meier Survival Curves for Rats Administered *t*-Butyl Alcohol in Drinking Water for 2 Years



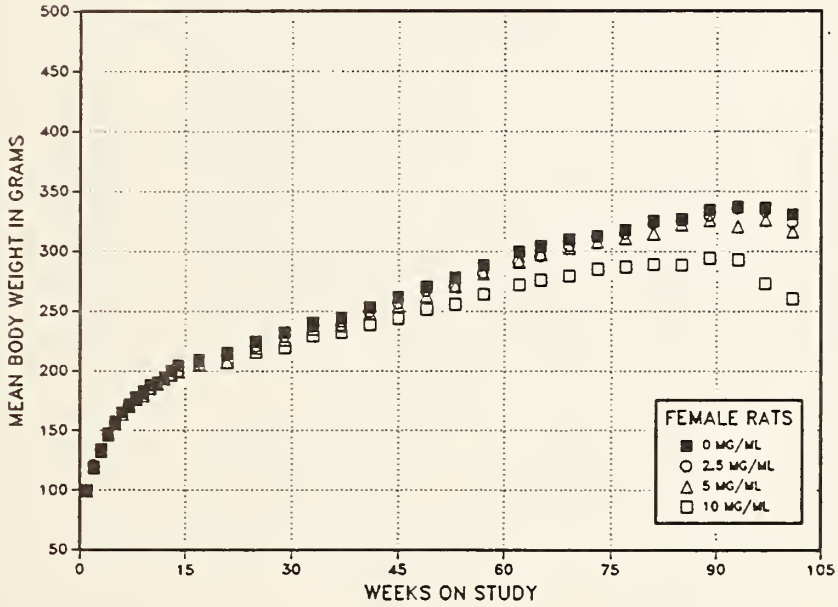


FIGURE 2
Growth Curves for Rats Administered *t*-Butyl Alcohol in Drinking Water for 2 Years

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

Weeks on Study	0 mg/mL		1.25 mg/mL			2.5 mg/mL			5 mg/mL		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	130	60	130	100	60	130	100	60	129	99	60
2	175	60	175	100	60	174	99	60	173	99	60
3	209	59	207	99	60	207	99	60	203	97	60
4	237	59	234	99	60	237	100	60	230	97	60
5	256	59	253	99	60	255	100	60	250	98	60
6	275	59	272	99	60	276	100	60	269	98	60
7	293	59	286	98	60	290	99	60	285	97	60
8	306	59	300	98	60	302	99	60	296	97	60
9	319	59	310	97	60	315	99	60	309	97	60
10	329	59	320	97	60	326	99	60	320	98	60
11	338	59	327	97	60	335	99	60	328	97	60
12	345	59	335	97	60	341	99	60	332	96	60
13	349	59	340	97	60	346	99	60	337	97	60
17	374	59	370	99	60	371	99	60	362	97	60
21	384	59	374	98	60	377	98	60	365	95	60
25	409	59	395	97	60	402	98	60	388	95	60
29	424	59	411	97	60	419	99	60	401	95	60
33	439	59	425	97	60	432	99	60	416	95	60
37	441	59	427	97	60	434	98	60	416	94	60
41	451	59	439	97	60	448	99	60	432	96	58
45	459	58	448	98	59	454	99	60	437	95	58
49	463	58	451	97	59	456	98	60	440	95	58
53	468	58	455	97	58	458	98	58	438	94	58
57	477	58	464	97	57	466	98	57	448	94	58
61	480	58	463	97	57	462	96	57	438	91	58
65	486	58	467	96	57	467	96	56	436	90	58
69[a]	481	48	464	96	47	458	95	46	430	89	48
73	484	47	464	96	47	454	94	44	422	87	46
77	479	45	464	97	45	451	94	41	424	88	45
81	469	39	447	95	42	419	89	35	377	80	40
85	468	34	459	98	36	433	92	29	388	83	29
89	468	25	440	94	30	412	88	24	400	86	18
93	481	19	433	90	23	430	89	13	395	82	13
97	462	16	417	90	16	406	88	8	385	83	5
101	454	12	387	85	10	374	83	4	344	76	2
Mean for weeks											
1-13	274		268	98		272	99		266	97	
14-52	427		416	97		421	99		406	95	
53-101	474		448	95		438	92		410	86	

[a] Interim evaluation occurred during week 66.

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

Weeks on Study	0 mg/mL Av. Wt. (g)	0 mg/mL No. of Survivors	2.5 mg/mL Av. Wt. (g)	2.5 mg/mL Wt. (% of controls)	2.5 mg/mL No. of Survivors	5 mg/mL Av. Wt. (g)	5 mg/mL Wt. (% of controls)	5 mg/mL No. of Survivors	10 mg/mL Av. Wt. (g)	10 mg/mL Wt. (% of controls)	10 mg/mL No. of Survivors
1	100	60	100	101	60	99	99	60	99	99	60
2	120	60	121	101	60	119	100	60	118	99	60
3	135	60	133	99	60	133	98	60	133	99	60
4	146	60	147	101	60	146	100	60	148	101	60
5	157	60	157	100	60	156	99	60	158	100	60
6	166	60	165	100	60	164	99	60	166	100	60
7	171	60	171	100	60	170	100	60	172	101	60
8	178	60	177	99	60	176	99	60	177	99	60
9	183	60	181	99	60	179	98	60	181	99	60
10	188	60	185	98	60	185	99	60	186	99	60
11	190	60	190	100	60	189	100	60	190	100	60
12	195	60	193	99	60	193	99	60	193	99	60
13	200	60	197	98	60	197	98	60	196	98	60
14	204	60	200	98	60	200	98	60	199	97	60
17	209	60	207	99	60	206	99	60	205	98	60
21	215	60	214	99	60	207	96	60	207	96	60
25	225	60	221	98	60	219	98	60	216	96	60
29	232	60	229	99	60	226	97	60	220	95	60
33	240	60	237	99	60	235	98	60	229	95	59
37	244	59	238	98	59	238	97	60	233	95	59
41	253	59	250	99	59	248	98	59	239	94	59
45	262	59	257	98	59	255	97	59	244	93	59
49	271	59	267	99	58	263	97	57	252	93	59
53	278	59	271	97	58	271	97	57	256	92	59
57	288	59	282	98	58	281	98	55	264	92	59
62	300	58	291	97	57	291	97	55	272	91	59
65	304	58	296	97	56	297	98	55	276	91	59
69[a]	310	48	305	98	46	303	98	43	280	90	48
73	313	48	312	100	45	308	99	43	285	91	48
77	318	47	315	99	44	311	98	42	287	90	47
81	326	45	323	99	41	315	97	41	289	89	45
85	327	42	326	100	39	322	99	37	288	88	43
89	335	38	330	99	34	326	97	36	294	88	32
93	337	33	336	100	29	321	95	33	293	87	24
97	336	32	333	99	29	326	97	30	273	81	21
101	331	29	324	98	28	316	96	26	261	79	17
Mean for weeks											
1-13	164		163	100		162	99		163	99	
14-52	236		232	99		230	98		224	95	
53-101	316		311	99		307	97		278	88	

[a] Interim evaluation occurred during week 66.

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the kidney, oral mucosa, mammary gland, and pancreatic islets. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analysis of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Kidney: At the 15-month extended evaluation, a renal tubule adenoma was observed in one 5 mg/mL male (Table 7); there was a significant dose-related increase in absolute and relative kidney weights in exposed females; exposed males exhibited a slight increase in absolute kidney weights, and relative kidney weights were significantly increased in 2.5 and 5 mg/mL males (Table F2). Also at 15 months, incidences and severities of mineralization of the kidney in 2.5 and 5 mg/mL males were greater than those in the controls, nephropathy was present in all males and females, and the severity of nephropathy was slightly increased in exposed groups of males and in 5 and 10 mg/mL females (Tables 7, 8, A5, and B5).

At the end of the study, the incidences of focal renal tubule hyperplasia and of adenoma were increased in exposed males and a carcinoma occurred in one 5 mg/mL male (Table 7). In females, renal tubule lesions were limited to hyperplasia in one 10 mg/mL female. Because of the increased incidence of these rare proliferative lesions in exposed males, additional step sections of residual formalin-fixed kidneys from all control and exposed males were prepared and examined microscopically. As a result of this extended evaluation, hyperplasia was identified in 11 additional control males, 13 additional 1.25 mg/mL males, 11 additional 2.5 mg/mL males, and 19 additional 5 mg/mL males; the trend is significant and the incidence in 5 mg/mL males is significant by pairwise comparison. Renal tubule adenoma was found in 7 additional control males, 8 additional 1.25 mg/mL males, 15 additional 2.5 mg/mL males, and 10 additional 5 mg/mL males; the trend is significant and the incidence in the 2.5 mg/mL group is significant by pairwise comparison. Renal tubule carcinoma was identified in two 1.25 mg/mL males and in one 2.5 mg/mL male from the extended evaluation. When the standard and extended evaluations were combined, the increased incidences of hyperplasia and of adenoma were dose related; the incidences of hyperplasia in 5 mg/mL males and of adenoma in 2.5 mg/mL males were significantly greater than those of the controls (Table 7). The increased incidence of adenoma in the 5 mg/mL males was also significant (P=0.044) when the animal with the adenoma observed at the 15-month extended evaluation was included in the statistical analysis.

Renal tubule hyperplasia is distinguished from foci of regeneration associated with spontaneous nephropathy because there is no thickening of tubule basement membranes and more disorganization and crowding, sometimes with stratification, of tubule epithelial cells with hyperplastic lesions. Adenomas of renal tubule epithelium are larger than hyperplastic lesions (five or more tubule diameters), lack definite tubule structure and dependence on a basement membrane, and are more structurally complex (Plate 1). Tubule epithelium in adenomas has some cellular atypia and, occasionally, evidence of mitotic activity. Tubule epithelial carcinomas are less discrete (i.e., more extensive and invasive) and have more anaplasia and cellular atypia than adenomas.

The severity of nephropathy was significantly increased in all exposed groups of females and in 5 mg/mL males at the end of the 2-year study (Tables 7 and 8). Microscopically, lesions consistent with nephropathy were thickened tubule and glomerular basement membranes, basophilic foci of regenerating renal tubule epithelium, intratubule protein casts, focal mononuclear inflammatory cell aggregates within areas of interstitial fibrosis and scarring, and glomerular sclerosis. Inflammation of the kidneys, also regarded as part of the nephropathy, was significantly increased in both 5 and 10 mg/mL females at the end of the 2-year study. Other lesions associated with nephropathy included mineralization, which was significantly increased in 5 mg/mL males, and transitional epithelial hyperplasia, which was significantly increased in 2.5 and 5 mg/mL males and in 10 mg/mL females. Hyperplasia, an increased number of layers or papillary projections of transitional epithelium lining the renal pelvis, occurs commonly with nephropathy but can be increased in treated groups with more severe nephropathy. There was no progression of the transitional epithelial

TABLE 7
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

Dose	0 mg/mL		1.25 mg/mL		2.5 mg/mL		5 mg/mL	
15-Month Interim Evaluation								
Single Sections (Standard Evaluation)								
Kidney[a]	10		10		10		10	
Mineralization[b]	1	(1.0)[c]	2	(1.0)	5	(1.8)	9**	(2.3)
Nephropathy	10	(2.4)	10	(2.7)	10	(2.8)	10	(2.6)
Step Sections (Extended Evaluation)								
Kidney	10		10		10		10	
Renal Tubule Hyperplasia	0		0		2		0	
Renal Tubule Adenoma	0		0		0		1	
2-Year Study								
Single Sections (Standard Evaluation)								
Kidney	50		50		50		50	
Nephropathy	49	(3.0)	49	(3.1)	50	(3.1)	50	(3.3)*
Transitional Epithelium, Hyperplasia	25	(1.7)	32	(1.7)	36**	(2.0)	40**	(2.1)
Mineralization	26	(1.0)	28	(1.1)	35	(1.3)	48**	(2.2)
Mineralization, Linear	0		5*	(1.0)	24**	(1.2)	46**	(1.7)
Renal Tubule, Hyperplasia	3	(1.7)	7	(1.7)	6	(2.0)	6	(1.7)
Renal Tubule Adenoma	1		3		4		2	
Renal Tubule Adenoma, multiple	0		0		0		1	
Renal Tubule Carcinoma	0		0		0		1	
Renal Tubule Adenoma or Carcinoma[d]	1		3		4		3	
Step Sections (Extended Evaluation)								
Kidney	50		50		50		50	
Renal Tubule, Hyperplasia	12	(2.3)	16	(2.3)	14	(2.2)	23*	(2.8)
Renal Tubule Adenoma	6		4		9		9	
Renal Tubule Adenoma, multiple	1		4		9**		2	
Renal Tubule Carcinoma	0		2		1		0	
Renal Tubule Adenoma or Carcinoma (combined)	7		10		18**		11	

(continued)

TABLE 7
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

Dose	0 mg/mL		1.25 mg/mL		2.5 mg/mL		5 mg/mL	
2-Year Study (continued)								
Standard and Extended Evaluations (Combined)								
Kidney	50		50		50		50	
Renal Tubule, Hyperplasia	14	(2.1)	20	(2.3)	17	(2.2)	25**	(2.7)
Renal Tubule Adenoma	7		7		10		10	
Renal Tubule Adenoma, multiple	1		4		9**		3	
Renal Tubule Carcinoma	0		2		1		1	
Renal Tubule Adenoma or Carcinoma (combined)	8		13		19**		13	

* Significantly different (P≤0.05) from the control group by the Fisher exact test (15-month interim evaluation) or by the logistic regression test (2-year study) for incidences. Severities of nephropathy are significantly different by the Mann-Whitney U test.
** (P≤0.01)
[a] Number of animals with kidney examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Historical incidence for 2-year NTP drinking water studies with untreated control groups (mean ± standard deviation): 1/277 (0.4% ± 0.9%); range 0%-2%

TABLE 8
Incidences of Nonneoplastic Lesions of the Kidney in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

Dose	0 mg/mL		2.5 mg/mL		5 mg/mL		10 mg/mL	
15-Month Interim Evaluation								
Kidney[a]	10		10		10		10	
Mineralization[b]	10	(2.8)[c]	10	(2.9)	10	(2.9)	10	(2.8)
Nephropathy	10	(1.5)	10	(1.4)	10	(2.0)	10	(1.8)
2-Year Study								
Kidney	50		50		50		50	
Inflammation, Suppurative	2	(1.0)	3	(1.3)	13**	(1.0)	17**	(1.1)
Mineralization	49	(2.6)	50	(2.6)	50	(2.7)	50	(2.9)
Nephropathy	48	(1.6)	47	(1.9)*	48	(2.3)**	50	(2.9)**
Renal Tubule, Hyperplasia	0		0		0		1	(1.0)
Transitional Epithelium, Hyperplasia	0		0		3	(1.0)	17**	(1.4)

* Significantly different (P≤0.05) from the control group by the logistic regression test (incidences) or by the Mann-Whitney U test (severity grades)
** (P≤0.01)
[a] Number of animals with kidney examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

hyperplasia in either the renal pelvis or the urinary bladder to benign or malignant neoplasms.

Mineralization, which is considered to be a component of nephropathy, was present in both the control and exposed groups of male rats (Table 7). A component of this mineralization included linear foci in the renal papilla that were limited to exposed males (0/50, 5/50, 24/50, 46/50). These foci consisted of distinctive linear deposits along radiating medullary collecting ducts (Plate 2). Foci of linear mineralization have been previously described as a lesion specifically associated with nephropathy attributed to increased accumulations of $\alpha_{2\mu}$-globulin in male rats. The more common pattern of mineral deposits at the junction of inner and outer stripes at the corticomedullary junction was observed in females and control males.

Oral Mucosa: Squamous cell papilloma or carcinoma (combined) occurred with a low incidence in exposed female rats (0/50, 2/50, 1/50, 2/50; Table B1). Although these are uncommon neoplasms, the increased incidences relative to the control group are neither significant nor dose related and are not considered to be related to the administration of *t*-butyl alcohol.

Mammary Gland: The incidences of adenoma, fibroadenoma, or carcinoma (combined) occurred with a significant negative trend in female rats (17/50, 16/50, 12/50, 10/50; Table B3) and the decrease was significant in 10 mg/mL females compared to that of the controls. The incidence of mammary gland carcinoma also occurred with a significant negative trend, but the decreases were not significant by pairwise comparison.

Pancreatic Islets: A significant negative trend occurred in the incidences of pancreatic islet adenoma or carcinoma (combined) in males (17/50, 15/49, 9/49, 6/49; Table A3).

Mice

13-Week Study

The deaths of two male and one female 40 mg/mL mice were attributed to exposure to *t*-butyl alcohol; all other deaths were considered unrelated to chemical administration (Table 9). The final mean body weight of males given 20 mg/mL was 14% lower than that of the controls, and that of males given 40 mg/mL was 25% lower than that of the controls. The final mean body weight of 40 mg/mL females was 15% lower than that of the controls. The mean body weight gains of 40 mg/mL males and females and of 20 mg/mL males were lower than those of the controls.

Water consumption by 20 and 40 mg/mL males was reduced during the first half of the study, but became greater than that by controls in the final 2 weeks of the study. Males given 5 mg/mL also showed an increase in water consumption at the end of the study. Water consumption by females given 20 and 40 mg/mL was reduced throughout most of the study, but was greater than that by controls at the end of the study. Exposure levels of 2.5, 5, 10, 20, or 40 mg/mL delivered average daily doses of approximately 350, 640, 1,590, 3,940, or 8,210 mg *t*-butyl alcohol/kg body weight to males and approximately 500, 820, 1,660, 6,430, or 11,620 mg/kg to females.

Table 9
Survival, Mean Body Weights, and Water Consumption of Mice in the 13-Week Drinking Water Study of *t*-Butyl Alcohol

Dose (mg/mL)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Water Consumption[c] Week 1	Week 13
Male							
0	9/10[d]	23.1 ± 0.3	38.0 ± 0.8	15.1 ± 0.5		4.1	4.5
2.5	10/10	22.2 ± 0.4	37.7 ± 0.9	15.5 ± 0.8	99	3.5	4.2
5	10/10	22.4 ± 0.5	38.2 ± 1.1	15.9 ± 0.9	101	3.6	7.2
10	10/10	22.6 ± 0.4	36.5 ± 0.9	13.9 ± 0.7	96	6.0	3.6
20	10/10	22.1 ± 0.5	32.7 ± 1.2**	10.6 ± 0.9**	86	3.4	7.4
40	4/10[e]	21.5 ± 0.4*	28.7 ± 1.0**	7.0 ± 1.1**	75	3.3	7.0
Female							
0	10/10	18.2 ± 0.4	29.6 ± 1.1	11.4 ± 1.0		3.8	8.7
2.5	9/10[f]	17.7 ± 0.5	30.5 ± 0.9	12.7 ± 0.9	103	3.7	5.9
5	10/10	17.0 ± 0.4	29.2 ± 0.6	12.3 ± 0.5	99	3.5	4.1
10	10/10	18.3 ± 0.4	30.7 ± 0.9	12.4 ± 0.9	104	3.9	4.2
20	9/10[g]	17.4 ± 0.4	27.7 ± 0.7	10.1 ± 0.6	94	3.5	11.0
40	6/10[h]	16.7 ± 0.2*	25.3 ± 0.5**	8.4 ± 0.3*	85	3.0	9.2

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Water consumption is expressed as grams of water consumed per animal per day.
[d] Week of death: 3
[e] Week of death: 4, 5, 7, 7, 9, 13
[f] Week of death: 12
[g] Week of death: 10
[h] Week of death: 2, 5, 9, 9

Clinical findings included emaciation, ataxia, and hypoactivity in 40 mg/mL males and emaciation in 40 mg/mL females.

A significant increase occurred in the segmented neutrophil count of 40 mg/mL males; however, the data were highly variable (Table G3). The erythrocyte count and hemoglobin and hematocrit values were minimally increased in 40 mg/mL males, and (less consistently) in 20 mg/mL males and females and 40 mg/mL females, suggesting hemoconcentration resulting from slight dehydration.

The absolute and relative kidney weights of 40 mg/mL females were significantly greater than those of the controls (Table F3).

Hyperplasia of the urinary bladder transitional epithelium was present in all male and three female mice given 40 mg/mL and in six 20 mg/mL male mice (Table 10). Chronic inflammation of the urinary bladder was found in all males and six females given 40 mg/mL and six 20 mg/mL males.

Hyperplasia of the transitional epithelium of the urinary bladder consisted of an increase in the thickness of the mucosal epithelium and in this study included both diffuse and more focal proliferative lesions. Diffuse hyperplastic lesions were generalized, with increased (two- or threefold) numbers of layers of epithelial cells in the mucosa. More focal hyperplastic lesions also had more epithelial layers, but often had a papillary appearance with finger-like projections of epithelium into the lumen. Inflammation consisted primarily of macrophages, lymphocytes, and plasma cells that were either diffuse or focal in the lamina propria. In some cases there were also numbers of neutrophils accompanying the chronic mononuclear inflammatory cells.

No significant differences in sperm morphology or motility or in the percentage of time spent in the various estrous cycles occurred during the 13-week study; however, estrous cycle length was significantly increased in 40 mg/mL females (Table H2).

Dose Selection Rationale

Mortality in male and female mice in the 13-week study precluded the use of 40 mg/mL in the 2-year study. The 20 mg/mL males in the 13-week study had a final mean body weight 86% of that of the control group, and minimal inflammation and transitional cell hyperplasia of the urinary bladder were observed in some of these males. The severity of these changes at this exposure was not considered sufficient to adversely affect survival in a 2-year study. Thus, 20 mg/mL was chosen as the high dose for the present 2-year mouse study.

TABLE 10
Incidences of Nonneoplastic Lesions of the Urinary Bladder of Mice in the 13-Week Drinking Water Study of *t*-Butyl Alcohol

Dose	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Male						
Urinary Bladder[a]	10	–[c]	–	10	10	10
Inflammation[b]	0	–	–	0	6** (1.3)[d]	10** (2.3)
Transitional Epithelial Hyperplasia	0	–	–	0	6** (1.3)	10** (2.0)
Female						
Urinary Bladder	10	1	–	–	10	9
Inflammation	0	0	–	–	0	6** (1.2)
Transitional Epithelial Hyperplasia	0	0	–	–	0	3 (2.0)

** Significantly different (P≤0.01) from the control group by the Fisher exact test
[a] Number of animals with urinary bladder examined microscopically
[b] Number of animals with lesion
[c] Urinary bladder not examined at this dose level
[d] Average severity of lesions in affected rats: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 11 and in the Kaplan-Meier survival curves (Figure 3). Survival of 20 mg/mL males was significantly lower than that of the controls. Because of reduced survival, the 15-month interim evaluation scheduled to be performed on 10 male and female mice was not conducted.

Body Weights, Water and Compound Consumption, and Clinical Findings

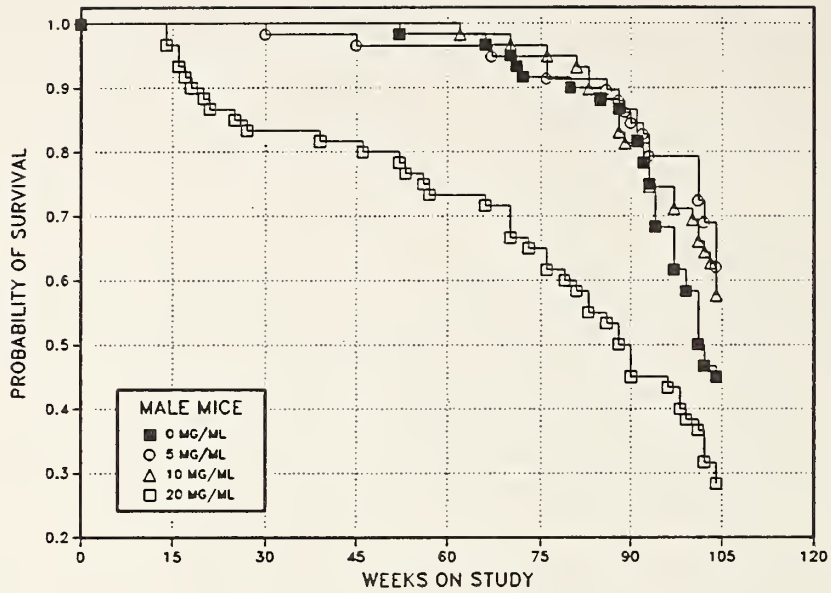
Beginning at about week 9, mean body weight gain of the 20 mg/mL males was lower than that of the control group, and the mean body weight of this group remained 5% to 10% lower than that of the controls until the final 10 weeks of the study. Final mean body weights and body weight gains of the remaining groups of exposed males were similar to those of the controls. The mean body weights of females given 20 mg/mL were 10% to 15% lower than those of the controls from week 13 through the end of the study, and their final mean body weight was 12% less than that of the controls (Figure 4, Tables 12 and 13). Throughout the study, the mean body weight of the 10 mg/mL females was about 6% lower than that of the controls, and the mean body weight of the 5 mg/mL females was slightly lower than that of the controls.

Water consumption by exposed groups of males and females was similar to that by controls (Tables J3 and J4). Exposure levels of 5, 10, or 20 mg/mL delivered average daily doses of approximately 540, 1,040, or 2,070 mg *t*-butyl alcohol/kg body weight to males and approximately 510, 1,020, or 2,110 mg/kg to females. There were no clinical findings that were considered related to chemical administration.

TABLE 11
Survival of Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Male				
Animals initially in study	60	60	60	60
Accidental deaths[a]	0	2	1	0
Moribund	20	14	19	21
Natural deaths	13	8	6	22
Animals surviving to study termination	27	36	34	17
Percent probability of survival at end of study[b]	45	62	58	28
Mean survival (days)[c]	676	665	678	538
Survival analysis[d]	P<0.001	P=0.077N	P=0.228N	P=0.007
Female				
Animals initially in study	60	60	60	60
Accidental deaths[a]	1	3	2	2
Moribund	13	14	13	12
Natural deaths	10	8	4	4
Animals surviving to study termination	36	35	41[e]	42
Percent probability of survival at end of study	61	61	71	72
Mean survival (days)	657	677	682	682
Survival analysis	P=0.121N	P=0.924N	P=0.298N	P=0.198N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.
[e] Includes one animal that died last week of the study



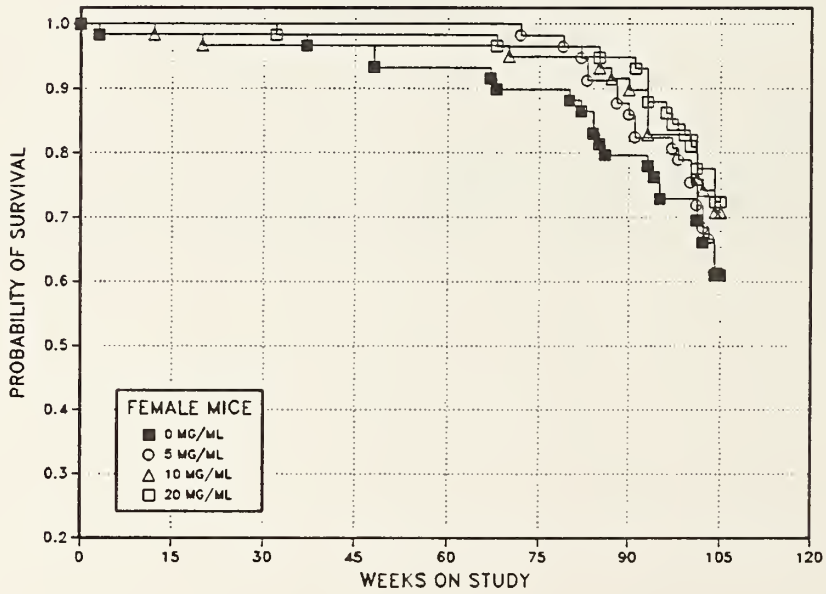


FIGURE 3
Kaplan-Meier Survival Curves for Mice Administered *t*-Butyl Alcohol in Drinking Water for 2 Years

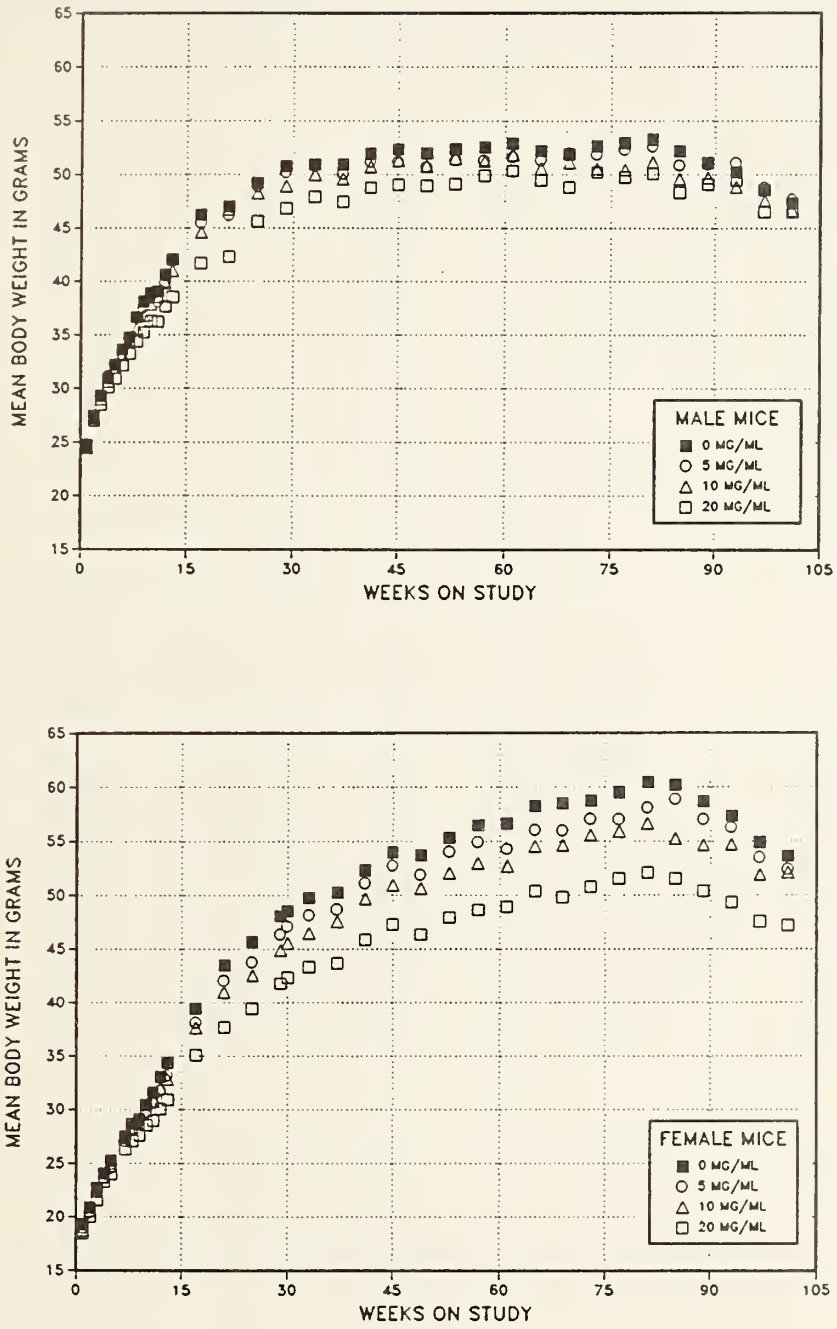


FIGURE 4
Growth Curves for Mice Administered *t*-Butyl Alcohol in Drinking Water for 2 Years

TABLE 12
Mean Body Weights and Survival of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

Weeks on Study	0 mg/mL Av. Wt. (g)	0 mg/mL No. of Survivors	5 mg/mL Av. Wt. (g)	5 mg/mL Wt. (% of controls)	5 mg/mL No. of Survivors	10 mg/mL Av. Wt. (g)	10 mg/mL Wt. (% of controls)	10 mg/mL No. of Survivors	20 mg/mL Av. Wt. (g)	20 mg/mL Wt. (% of controls)	20 mg/mL No. of Survivors
1	24.7	60	24.8	100	60	24.6	100	60	24.4	99	60
2	27.5	60	27.4	100	60	27.3	99	60	27.0	98	60
3	29.3	60	29.3	100	60	29.0	99	60	28.5	97	60
4	31.0	60	31.2	101	60	30.7	99	60	30.1	97	60
5	32.2	60	32.3	100	60	32.0	99	60	30.9	96	60
6	33.7	60	33.2	99	60	33.2	99	60	32.2	96	60
7	34.8	60	34.7	100	60	34.6	99	60	33.2	95	60
8	36.7	60	36.6	100	59	35.6	97	60	34.4	94	60
9	38.1	60	37.5	98	59	36.8	97	60	35.2	92	60
10	38.9	60	38.5	99	59	37.9	97	60	36.3	93	60
11	39.0	60	38.1	98	58	38.5	99	59	36.2	93	60
12	40.7	60	39.9	98	58	39.8	98	59	37.7	93	60
13	42.0	60	41.9	100	58	41.0	98	59	38.5	92	60
17	46.2	60	45.5	99	58	44.6	97	59	41.7	90	55
21	47.0	60	46.2	98	58	46.7	99	59	42.3	90	52
25	49.2	60	48.9	99	58	48.3	98	59	45.6	93	51
29	50.7	60	50.2	99	58	48.9	96	59	46.9	93	50
33	50.9	60	50.7	100	57	50.0	98	59	47.9	94	50
37	51.0	60	50.1	98	57	49.6	97	59	47.4	93	50
41	51.9	60	51.2	99	57	50.8	98	59	48.8	94	49
45	52.3	60	51.2	98	56	51.3	98	59	49.1	94	49
49	52.0	60	50.7	98	56	50.8	98	59	49.0	94	48
53	52.4	59	51.3	98	56	51.5	98	59	49.1	94	46
57	52.5	59	51.3	98	56	51.2	98	59	49.9	95	44
61	52.9	59	51.6	98	56	51.9	98	59	50.3	95	44
65	52.2	59	51.4	99	56	50.6	97	58	49.5	95	44
69	51.9	58	52.0	100	55	51.1	99	58	48.9	94	43
73	52.7	55	51.9	99	55	50.5	96	57	50.2	95	40
77	52.9	55	52.3	99	53	50.4	95	56	49.7	94	37
81	53.3	54	52.6	99	53	51.2	96	55	50.1	94	36
85	52.1	53	50.8	98	53	49.6	95	52	48.3	93	33
89	51.1	52	50.9	100	50	49.7	97	48	49.1	96	30
93	50.2	45	51.1	102	46	48.8	97	44[a]	49.5	99	27[a]
97	48.6	37	48.8	100	46	47.5	98	42	46.5	96	26
101	47.3	34	47.8	101	44	46.5	98	41	46.6	99	23
Mean for weeks											
1-13	34.5		34.3	99		33.9	98		32.7	95	
14-52	50.1		49.4	99		49.0	98		46.5	93	
53-101	51.5		51.1	99		50.0	97		49.1	95	

[a] The number of animals weighed for this week is fewer than the number of animals surviving.

TABLE 13
Mean Body Weights and Survival of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

Weeks on Study	0 mg/mL Av. Wt. (g)	0 mg/mL No. of Survivors	5 mg/mL Av. Wt. (g)	5 mg/mL Wt. (% of controls)	5 mg/mL No. of Survivors	10 mg/mL Av. Wt. (g)	10 mg/mL Wt. (% of controls)	10 mg/mL No. of Survivors	20 mg/mL Av. Wt. (g)	20 mg/mL Wt. (% of controls)	20 mg/mL No. of Survivors
1	19.3	60	19.0	98	60	18.8	97	60	18.5	96	60
2	20.9	60	20.4	98	60	20.6	99	60	20.0	96	60
3	22.7	59	22.3	98	60	22.4	99	60	21.6	95	60
4	24.1	59	23.7	98	60	23.7	98	60	23.3	97	60
5	25.2	59	24.6	98	60	24.8	98	60	24.0	95	60
7	27.5	59	27.1	99	60	27.4	100	60	26.3	96	60
8	28.7	59	28.2	98	60	28.3	99	60	27.1	94	60
9	29.1	59	28.9	99	60	28.8	99	60	27.6	95	60
10	30.5	59	29.8	98	60	29.9	98	60	28.6	94	59
11	31.6	59	30.7	97	59	30.8	98	60	29.0	92	59
12	33.0	59	31.8	96	59	32.0	97	60	30.1	91	58
13	34.4	59	33.2	97	59	32.9	96	59	30.9	90	58
17	39.4	59	38.1	97	59	37.7	96	59	35.1	89	58
21	43.5	59	42.0	97	59	41.0	94	58	37.7	87	58
25	45.7	58	43.8	96	59	42.5	93	58	39.5	86	58
29	48.1	58	46.4	97	59	44.9	93	58	41.8	87	58
30	48.5	58	47.1	97	59	45.6	94	58	42.3	87	58
33	49.8	58	48.1	97	59	46.5	93	58	43.3	87	57
37	50.3	58	48.7	97	59	47.5	94	58	43.7	87	57
41	52.3	57	51.1	98	59	49.7	95	58	45.9	88	57
45	54.0	57	52.7	98	58	51.0	94	58	47.3	88	57
49	53.7	55	51.9	97	58	50.6	94	58	46.3	86	57
53	55.3	55	54.0	98	57	52.0	94	58	47.9	87	57
57	56.5	55	54.9	97	57	53.0	94	58	48.6	86	57
61	56.6	55	54.3	96	57	52.7	93	58	48.9	86	57
65	58.2	55	56.0	96	57	54.5	94	57	50.4	87	57
69	58.5	53	56.0	96	57	54.6	93	57	49.8	85	56
73	58.8	53	57.1	97	56	55.6	95	55	50.8	86	56
77	59.5	53	57.0	96	56	55.9	94	55	51.5	87	56
81	60.5	52	58.1	96	55	56.7	94	55	52.1	86	56
85	60.2	48	58.9	98	52	55.2	92	55	51.6	86	56
89	58.7	47	57.1	97	50	54.7	93	53	50.4	86	55
93	57.3	47	56.3	98	47	54.7	96	49	49.4	86	53
97	54.9	43	53.5	97	46	51.9	95	48	47.5	87	50
101	53.6	43	52.4	98	43	52.1	97	46	47.2	88	46
Mean for weeks											
1-13	27.3		26.6	98		26.7	98		25.6	94	
14-52	48.5		47.0	97		45.7	94		42.3	87	
53-101	57.6		55.8	97		54.1	94		49.7	86	

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms of the thyroid gland and nonneoplastic lesions of the thyroid gland, urinary bladder, harderian gland, and liver. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analysis of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented Appendix C for male mice and Appendix D for female mice.

Thyroid Gland: The incidence of follicular cell adenoma was marginally increased in 10 mg/mL males and a follicular cell carcinoma was present in one male in the 20 mg/mL group (Tables 14 and C3). In 20 mg/mL females, the incidence of follicular cell adenoma was significantly greater than that of the controls and occurred bilaterally in one female in this exposure group (Tables 14 and D3). The incidences of follicular cell hyperplasia were significantly increased in all groups of exposed males and in 10 and 20 mg/mL females (Tables 14, C5, and D5).

Follicular cell hyperplasia consisted of foci with increased numbers of closely packed follicular epithelial cells, sometimes with minimal papillary folds (Plate 3). Morphologically, the hyperplastic lesions in mice treated with *t*-butyl alcohol were similar to spontaneous thyroid follicular hyperplasias observed in untreated mice, but with increased incidence in treated groups. Follicular cell adenomas of the thyroid gland were more complex structures than hyperplastic foci, and the follicular epithelial cells in adenomas had more atypical features and pleomorphism (e.g., variations in size, nuclear-to-cytoplasmic ratio, or nuclear chromatin pattern) than occurred in the hyperplastic lesions (Plate 4). The one follicular cell carcinoma in a 20 mg/mL male formed obvious solid cellular masses lacking lumina. Cells in the carcinoma had more atypia and pleomorphism than did the follicular epithelium in the adenomas. There was increased connective tissue around the nests of malignant cells in the carcinoma.

Urinary Bladder: The incidences of chronic inflammation were significantly increased in 20 mg/mL males and females and the incidence of transitional epithelial hyperplasia was significantly increased in 20 mg/mL males compared to those of the controls (Tables 15, C5, and D5). Three 20 mg/mL females also had transitional epithelial hyperplasia. Hyperplasia of the transitional epithelium of the urinary bladder consisted of both generalized, increased numbers of cell layers in the mucosal epithelium and of more papillary lesions with finger-like projections of thickened mucosal epithelium into the lumen. Chronic inflammation was usually concomitant with hyperplasia. Inflammatory cells included macrophages, lymphocytes, and plasma cells in the lamina propria. There was no progression of the transitional epithelial hyperplasia of the urinary bladder to neoplasia.

Liver: The incidence of hepatocellular carcinoma was significantly decreased in 20 mg/mL females (25/59, 26/60, 22/59, 12/60); however, the incidence of hepatocellular adenoma or carcinoma (combined) was similar in all groups of females (Table D3). The incidence of hepatocellular carcinoma was marginally increased in 10 mg/mL males and the combined incidence of adenoma or carcinoma was increased in the control and exposed groups of males except the 20 mg/mL group. The high incidence of hepatocellular neoplasms observed in male (81%) and female (69%) control mice is probably related to the increased body weights observed in these groups (Figure 4). The association between increased hepatocellular neoplasm incidence and increased body weights in $B6C3F_1$ mice has been well documented (Haseman, 1992; Haseman *et al.*, 1994). The incidence of fatty change was significantly increased in 20 mg/mL males (12/59, 5/60, 8/59, 29/59). Fatty change consisted of noticeable numbers of usually colorless, smoothly rounded intracytoplasmic vacuoles within hepatocytes. Fatty change of hepatocytes is a relatively mild, nonspecific response to various metabolic derangements.

Harderian Gland: The incidence of adenoma or carcinoma (combined) of the harderian gland was significantly decreased in all exposed males compared to that of the controls (10/60, 3/60, 3/60, 1/60). The rate of 17% in the control group from this study is high compared to the rates that occurred in controls from three other NTP drinking water studies (range: 6%–12%) and the rates in the exposed groups are not unusually low. The biological significance of these findings is uncertain.

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Thyroid Gland in Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

Dose	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Male				
Thyroid Gland[a]	60	59	59	57
Follicular Cell, Hyperplasia[b]	5 (1.2)[c]	18** (1.6)	15* (1.4)	18** (2.1)
Follicular Cell Adenoma				
Overall rate[d]	1/60 (2%)	0/59 (0%)	4/59 (7%)	1/57 (2%)
Adjusted rate[e]	3.6%	0.0%	10.1%	5.9%
Terminal rate[f]	0/27 (0%)	0/36 (0%)	2/34 (6%)	1/17 (6%)
First incidence (days)	727	–[h]	616	728 (T)
Logistic regression test[g]	P=0.300	P=0.439N	P=0.186	P=0.672
Follicular Cell Adenoma or Carcinoma[i]				
Overall rate	1/60 (2%)	0/59 (0%)	4/59 (7%)	2/57 (4%)
Adjusted rate	3.6%	0.0%	10.1%	8.7%
Terminal rate	0/27 (0%)	0/36 (0%)	2/34 (6%)	1/17 (6%)
First incidence (days)	727	–	616	580
Logistic regression test	P=0.144	P=0.439N	P=0.186	P=0.386
Female				
Thyroid Gland	58	60	59	59
Follicular Cell, Hyperplasia	19 (1.8)	28 (1.9)	33* (1.7)	47** (2.2)
Follicular Cell Adenoma[j]				
Overall rate	2/58 (3%)	3/60 (5%)	2/59 (3%)	9/59 (15%)
Adjusted rate	5.6%	8.6%	4.9%	19.6%
Terminal rate	2/36 (6%)	3/35 (9%)	2/41 (5%)	6/42 (14%)
First incidence (days)	729 (T)	729 (T)	729 (T)	646
Logistic regression test	P=0.011	P=0.487	P=0.647N	P=0.039

* Significantly different (P≤0.05) from the control group by the logistic regression test
** P≤0.01
(T)Terminal sacrifice
[a] Number of animals with thyroid gland examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Number of animals with neoplasms per number of animals necropsied
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal. A lower incidence in a dose group is indicated by N.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence for 2-year NTP drinking water studies with untreated control groups (mean ± standard deviation): 4/240 (1.7% ± 0.5%); range 1%-2%
[j] Historical incidence: 8/238 (3.4% ± 2.2%); range 0%-5%

TABLE 15
Incidences of Nonneoplastic Lesions of the Urinary Bladder in Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

Dose	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Male				
Urinary Bladder[a]	59	59	58	59
Inflammation, Chronic[b]	0	3 (1.7)[c]	1 (1.0)	37** (2.4)
Transitional Epithelium, Hyperplasia	1 (2.0)	3 (1.7)	1 (1.0)	17**(1.8)
Female				
Urinary Bladder	59	60	59	57
Inflammation, Chronic	0	0	0	4* (2.0)
Transitional Epithelium, Hyperplasia	0	0	0	3 (1.0)

* Significantly different (P≤0.05) from the control group by the logistic regression test
** P≤0.01
[a] Number of animals with urinary bladder examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

GENETIC TOXICOLOGY

t-Butyl alcohol (100 to 10,000 μg/plate) did not induce mutations in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537 with or without induced rat or hamster liver S9 (Table E1; Zeiger *et al.*, 1987). Results of a mouse lymphoma cell mutation test were also considered to be negative, although a small increase in mutant colonies was observed in a single trial at the highest dose tested (5,000 μg/mL) in the absence of S9 (Table E2; McGregor *et al.*, 1988). McGregor *et al.* (1988) presented an additional trial conducted without S9 that showed no increase in mutant colonies at any of the doses tested; that trial is not included in Table E2 because it did not meet quality control standards for the assay. The two trials conducted with S9 are clearly negative. In cytogenetic tests with cultured Chinese hamster ovary cells, *t*-butyl alcohol at doses up to 5,000 μg/mL did not induce sister chromatid exchanges (Table E3) or chromosomal aberrations (Table E4), with or without S9. In the sister chromatid exchange test without S9, a weakly positive result was obtained in one trial but it was not reproduced in a second trial. Neither trial conducted with S9 showed an increase in sister chromatid exchanges and the results of this test were considered negative. No cytotoxic effects were noted in the cultured Chinese hamster ovary cell experiments, with one exception. In the chromosomal aberrations test, the dose of 5,000 μg/mL in one of two trials performed with S9 produced toxicity severe enough to allow only 13 cells to be analyzed for aberrations, rather than the usual 100 cells per dose point.

In vivo, no increase in the frequency of micronucleated normochromatic erythrocytes was observed in male or female mice administered *t*-butyl alcohol in drinking water for 13 weeks (Table E5). In addition, no effect on the percentage of polychromatic erythrocytes in the total erythrocyte population was noted, an indication that *t*-butyl alcohol was not toxic to bone marrow cells.

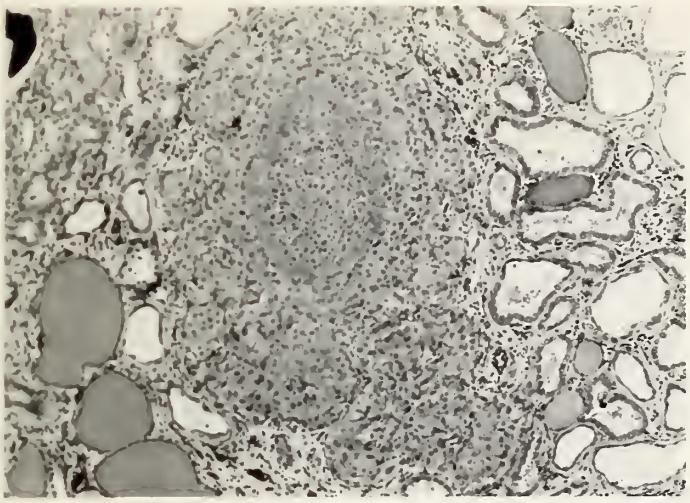


Plate 1
Kidney from a male F344/N rat exposed to 5 mg/mL *t*-butyl alcohol in drinking water for 2 years (rat died on day 679 of the study). Adenoma consists of a solid mass of proliferated renal tubule epithelium with central necrotic cells. H&E; 25×

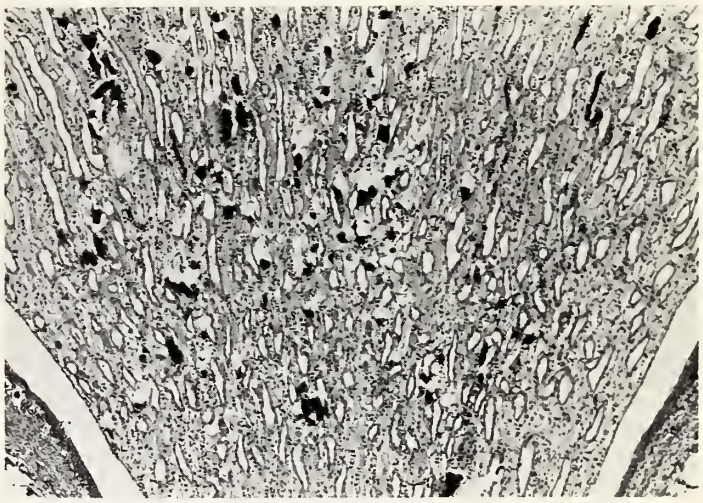


Plate 2
Kidney from a male F344/N rat exposed to 5 mg/mL *t*-butyl alcohol in drinking water for 2 years (rat evaluated at 15 months). Linear mineralization of the renal medulla. H&E; 16×

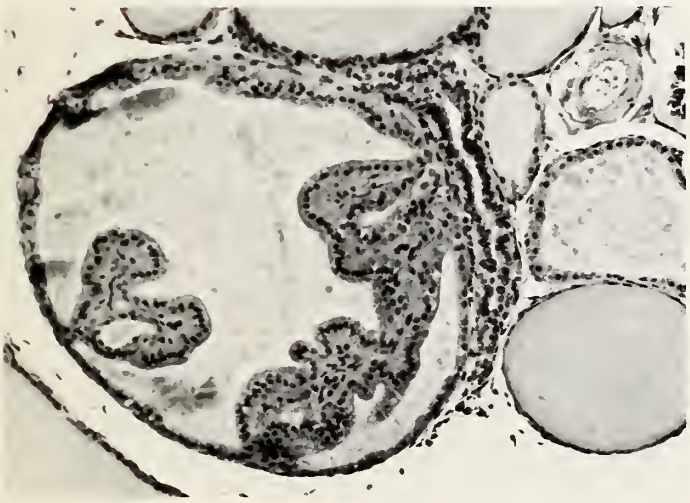


Plate 3
Thyroid gland from a female $B6C3F_1$ mouse exposed to 20 mg/mL *t*-butyl alcohol in drinking water for 2 years (mouse died on day 729 of the study). Hyperplasia of follicular epithelium with papillary extension into the lumen. H&E; 45×

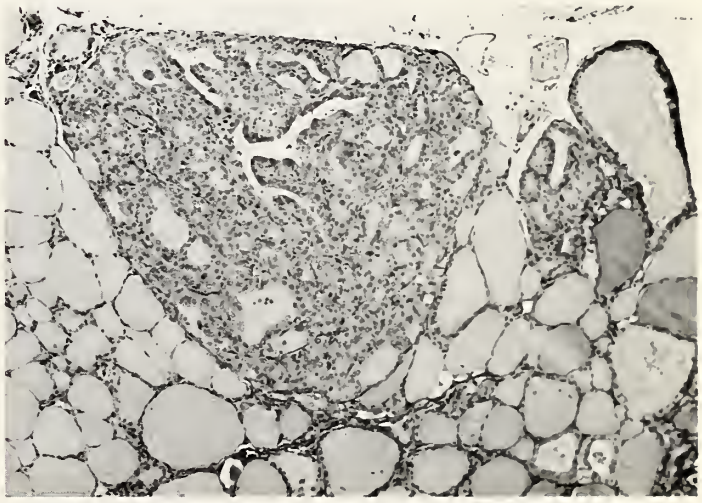


Plate 4
Thyroid gland from a male $B6C3F_1$ mouse exposed to 20 mg/mL *t*-butyl alcohol in drinking water for 2 years (mouse died on day 728 of the study). Follicular cell adenoma with complex architecture of follicular and solid cell structures. H&E; 25×

DISCUSSION AND CONCLUSIONS

t-Butyl alcohol is widely used in the manufacture of perfumes and cosmetics and may be used in the production of methyl tertiary butyl ether, a gasoline additive. The National Cancer Institute nominated *t*-butyl alcohol for toxicology and carcinogenicity studies as a result of a review of chemicals found in drinking water. It was selected for study because of its large annual production and potential for human exposure.

The primary evidence for the acute toxicity of *t*-butyl alcohol in experimental animals is related to signs of alcoholic intoxication including hypoactivity, ataxia, and hyperactivity, all of which were observed in rats and mice in the present 13-week studies. Treatment-related mortality occurred at the 40 mg/mL concentration in male and female rats and mice, and mean body weight gains of these groups were significantly lower than those of the controls. Slightly lower mean body weight gains were also present in male rats and male mice from the 10 mg/mL and 20 mg/mL groups. In addition to lower mean body weights, evidence of decreased palatability of the dosed water was reflected by the reduced water consumption by exposed groups of rats and by 20 and 40 mg/mL groups of mice during the first week of the studies. The minimal increase in serum alanine aminotransferase activity in all exposed groups of female rats was accompanied by significant increases in absolute and relative liver weights suggesting some liver toxicity in these animals. There was a minimal increase in sorbitol dehydrogenase activity in 10 and 20 mg/mL male rats at week 13, but no biologically significant change in liver weight occurred.

The principal treatment-related histopathologic findings in the 13-week studies were in the urinary bladder of rats and mice and in the kidney of rats. Treatment-related lesions in the urinary bladder were limited to the 20 and 40 mg/mL groups of male rats and mice and the 40 mg/mL groups of female rats and mice and consisted of transitional cell hyperplasia and inflammation of the bladder mucosa. For both male rats and male mice, the incidence and severity of the urinary bladder lesions were higher than that observed for females, and the no-effect level was lower. In rats, the transitional cell hyperplasia and inflammation may have been related to urinary bladder calculi, which were observed grossly; calculi were not identified in mice. Kidney lesions in female rats were limited to an increased incidence of nephropathy (renal tubule epithelial regeneration) in exposed groups. In male rats given *t*-butyl alcohol, the increased number and size of protein droplets in the kidney and the enhanced severity of renal tubule epithelial regeneration were consistent with the lesions reported for chemical-induced hyaline droplet nephropathy (Baetcke *et al.*, 1991).

The selection of 5 mg/mL for male rats and 10 mg/mL for female rats as the high exposure levels in the 2-year study was primarily based on the lower body weight gain observed in the 10 and 20 mg/mL males and in the 40 mg/mL females in the 13-week study. The accumulation of hyaline droplets and slight increase in the severity of renal tubule epithelial regeneration in the 2.5 and 5 mg/mL males and the increased incidence of renal tubule epithelial regeneration in the 10 mg/mL females were not considered to have a potentially adverse effect on survival in the 2-year study. The selection of 20 mg/mL as the high exposure level for mice in the 2-year study was based on mortality and on the lower body weight gain, especially of males, at the 40 mg/mL exposure level in the 13-week study. The minimal inflammation and hyperplasia of the urinary bladder in 6/10 male mice in the 20 mg/mL group were not considered to be effects that would adversely affect survival in the 2-year study.

Although the survival rate of the male rat control group in the 2-year study was relatively low, it was similar to that observed in other concurrent control groups and reflects the general trend toward decreased survival in control male F344/N rats in NTP studies (Haseman and Rao, 1992). Survival of the 5 mg/mL males was significantly lower than that of the controls. However, approximately 60% of the 2.5 and 5 mg/mL groups of male rats survived through week 85. Although survival among exposed female rats was lower than that of the controls, especially in the 10 mg/mL group, more than 50% of the females in each group survived through week 85. Therefore, survival of male and female rats was

considered adequate for the detection of a potential carcinogenic effect. Reduced survival in exposed male and female rats was probably related to the increased severity of nephropathy.

The survival of 20 mg/mL male mice in the 2-year study was significantly lower than that of the controls due to the nine early deaths in this group between weeks 14 and 25. The early deaths and high incidences of urinary bladder lesions in the 20 mg/mL group indicate that this concentration was probably excessive for male mice, although the cause of the early deaths is not known. However, since 50% of this group survived through week 89, the study in male mice was considered adequate for the assessment of carcinogenicity. Survival of female mice was similar to that of the controls, and the study in female mice was also regarded as adequate for the detection of carcinogenicity.

The principal effects resulting from 2 years of exposure to *t*-butyl alcohol in drinking water were in the kidney of male and female rats and in the thyroid gland and urinary bladder of male and female mice. In the standard histopathologic evaluation of the kidney in male rats from the 2-year study, there were slight increases in the incidences of proliferative lesions (hyperplasia, adenoma, and carcinoma) in exposed male rats. Subsequent evaluation of additional step sections of the kidney of male rats confirmed these increases in the incidences of renal tubule hyperplasia and adenoma as well as an increased incidence of multiple renal tubule adenoma in exposed groups. As in other studies in which the step-section procedure was used, additional proliferative lesions were also observed in the control group. The extended evaluation of the kidney also identified carcinomas in two additional males in the 1.25 mg/mL group and in one additional male in the 2.5 mg/mL group.

No incidences of renal tubule adenoma or carcinoma were observed in 227 control male rats in the four studies composing the recent NTP historical control database for drinking water studies. Although the database is small, the absence of renal tubule neoplasms is an indication of the rarity of these neoplasms in male rats. When the larger historical control database for feed studies is considered, the incidence of renal tubule adenoma or carcinoma (combined) is still only 15/1,350 (1.1%) and that of carcinoma alone is only 6/1,350 (0.4%). Although the increased incidence of renal tubule adenoma or carcinoma (combined) in the 2.5 mg/mL males was significant, the increase in the 5 mg/mL males was not statistically significant, possibly due to the increased toxicity at this exposure level. In the combined standard and extended evaluation, there were a total of four male rats with carcinoma in the exposed groups. In previous NTP studies using this method of extended evaluation, the incidence of carcinoma in male rats was 1/599 among 12 control groups (Eustis *et al.*, 1994). The pathogenesis of proliferative lesions of renal tubule epithelium is generally considered to follow a progression from hyperplasia to adenoma to carcinoma (Hard, 1986). When the results of the standard and extended evaluations were combined, the incidence of renal tubule hyperplasia and the combined incidence of adenoma and carcinoma were increased in all exposed groups. The increased incidence of hyperplasia was significant in the 5 mg/mL group, and the increased incidence of adenoma was significant in the 2.5 mg/mL group. The increased incidence of adenoma was significant (P=0.44) in the 5 mg/mL group if the animal with the adenoma from the 15-month extended evaluation was included in the statistical analysis. Taken together, these findings for the kidney are considered to indicate some evidence of carcinogenicity in male rats.

The treatment-related increase in the severity of nephropathy in male and female rats was characterized by an exacerbation of the typical spectrum of morphological features (tubule epithelial regeneration, protein casts, and transitional cell hyperplasia) seen in the kidney of control rats at the end of a 2-year study (Peter *et al.*, 1986). However, the presence of linear foci of mineralization in the renal medulla of exposed groups of male rats in this study is a feature consistently reported for hyaline droplet nephropathy (Baetcke *et al.*, 1991). The specific kidney lesions observed in male rats from the 13-week study and the increase in proliferative lesions of the renal tubule in male rats after 2 years of exposure to *t*-butyl alcohol have been reported for a number of chemicals associated with the accumulation of $\alpha_{2\mu}$-globulin in phagolysosomes of the renal tubule epithelium (NTP, 1990; Stonard *et al.*, 1986). Reversible binding of chemicals or their metabolites with $\alpha_{2\mu}$-globulin has been proposed to affect its normal lysosomal catabolism and result in its accumulation in the renal tubule epithelium (Lock et al., 1987). Although the morphology and staining

characteristics of the hyaline droplets in the kidney of male rats in the present 13-week study are similar to those which have been reported to consist of $\alpha_{2\mu}$-globulin, the biochemical identity of the hyaline droplets was not determined. It was also not confirmed in this study if there was binding of *t*-butyl alcohol to the protein in the hyaline droplets.

Chemicals which cause accumulation of hyaline droplets also result in cytotoxicity of the renal tubule epithelium evidenced by cellular necrosis and formation of granular casts of cell debris in tubules; increased cell proliferation in the renal tubules has also been demonstrated (Charbonneau *et al.*, 1987, 1989). In a retrospective analysis of the 13-week study, cell proliferation in the renal tubule epithelium, assessed by proliferating cell nuclear antigen, was not increased above control values in the 2.5 or 5 mg/mL groups of male rats. There was a slight increase in the 10 mg/mL group and a significant increase in the 20 mg/mL group (Takahashi *et al.*, 1993). With chronic chemical administration, a sustained increased rate of cellular proliferation in the kidney has been proposed to promote the development of neoplasms from spontaneously initiated cells (Charbonneau *et al.*, 1987). *t*-Butyl alcohol caused less cytotoxicity in prechronic studies and a less prominent neoplasm response after 2 years than has been observed with other chemicals which have caused hyaline droplet nephropathy (NTP, 1987, 1989, 1990). There was no morphologic evidence of extensive cell necrosis (granular cast formation) with *t*-butyl alcohol exposure, although the increased severity of nephropathy (regeneration) suggests a treatment-related cytotoxicity in exposed rats. However, the increased severity of nephropathy also seen in females suggests that the mechanism for renal cytotoxicity was not limited to an increased accumulation of $\alpha_{2\mu}$-globulin.

In the 2-year study, the incidence of follicular cell hyperplasia of the thyroid gland was significantly increased in all exposed groups of male mice and in the 10 and 20 mg/mL groups of female mice; the incidence of follicular cell adenoma was significantly increased in 20 mg/mL females; and a follicular cell carcinoma was observed in one 20 mg/mL male. Proliferation of thyroid gland follicular cells is generally considered to follow a progression from hyperplasia to adenoma and carcinoma. The increased incidence of follicular cell adenoma in 20 mg/mL female mice was statistically significant, and the rate of 15% exceeds the maximum rate of 5% observed in controls in previous NTP drinking water studies. In addition, there were concomitant significant increases in incidences of follicular cell hyperplasia in the 10 and 20 mg/mL females. These findings in female mice constitute some evidence of carcinogenic activity for *t*-butyl alcohol.

Although male mice did not demonstrate a significant increase in the incidence of benign or malignant follicular cell neoplasms, the incidence of follicular cell hyperplasia was significantly increased in all exposed groups. The incidence of adenoma of 7% in 10 mg/mL male mice, while not statistically significant, exceeds the maximum rate of 2% observed historically in untreated NTP drinking water controls, and the incidence of 4% in the 20 mg/mL group may have been related to the reduced survival in this group. For these reasons, and considering the thyroid follicular cell neoplasm response in females, equivocal evidence of carcinogenic activity in male mice is indicated.

The development of proliferative lesions may have been related to a direct effect of *t*-butyl alcohol on the thyroid gland; however, another possible mechanism is through the induction of hepatic microsomal enzymes resulting in altered thyroid function and neoplasia (Hill *et al.*, 1989; McClain, 1989). The thyroid hormone thyroxine (T4) is metabolized by conjugation with glucuronic acid and is excreted in the bile. Enhanced glucuronidation activity resulting in increased metabolism of T4 leads to the increased production of thyroid stimulating hormone, which triggers the development of follicular cell hyperplasia and neoplasia in rodents. While a similar mechanism for the proliferative lesions in the thyroid gland of mice could have been present in this 2-year study, there was no morphologic evidence of follicular cell hyperplasia at 13 weeks. Also, this mechanism is usually accompanied by liver hypertrophy or other evidence of enzyme induction, which was not present in this study. Tertiary alcohols including *t*-butyl alcohol, though not readily metabolized, have been shown to become conjugated and form glucuronides (Williams, 1959). It is possible that this increased enzymatic activity could result in an increase in glucuronidation of T4. Further studies are required to determine if this mechanism may be involved in the development of proliferative thyroid lesions associated with the administration of *t*-butyl alcohol.

There were no effects in the urinary bladder of rats related to the administration of *t*-butyl alcohol after 2 years of exposure to concentrations that were lower than those that caused hyperplasia in the 13-week study. Mice developed transitional cell hyperplasia and inflammation of the urinary bladder in the 2-year study at the same exposure levels that were associated with these lesions at 13 weeks. The cause of the urinary bladder lesions was not determined. Urinary calculi were not observed grossly in mice. However, the presence of other factors which may cause similar urinary bladder lesions in mice, such as microcrystal formation or decreased urine osmolality (West *et al.*, 1984), were not assessed in this study. There was no evidence of progression of the urinary bladder transitional epithelial hyperplasia to benign or malignant neoplasia.

Conclusions

Under the conditions of these 2-year drinking water studies, there was *some evidence of carcinogenic activity** of *t*-butyl alcohol in male F344/N rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was *no evidence of carcinogenic activity* in female F344/N rats receiving 2.5, 5, or 10 mg/mL *t*-butyl alcohol. There was *equivocal evidence of carcinogenic activity* of *t*-butyl alcohol in male $B6C3F_1$ mice based on the marginally increased incidences of follicular cell adenoma or carcinoma (combined) of the thyroid gland. There was *some evidence of carcinogenic activity* of *t*-butyl alcohol in female $B6C3F_1$ mice based on increased incidences of follicular cell adenoma of the thyroid gland.

Exposure to *t*-butyl alcohol was associated with mineralization and renal tubule hyperplasia in male rats, transitional epithelial hyperplasia and increased severity of nephropathy of the kidney in male and female rats, follicular cell hyperplasia of the thyroid gland in male and female mice, and chronic inflammation and hyperplasia of the urinary bladder in male mice and to a lesser extent in female mice.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

REFERENCES

Aarstad, K., Zahlsen, K., and Nilsen, O.G. (1985). Inhalation of butanols: Changes in the cytochrome P-450 enzyme system. *Arch. Toxicol.* (Suppl. 8), 418-421.

Anderson, R.A., Jr., Reddy, J.M., Joyce, C., Willis, B.R., Van der Ven, H., and Zaneveld, L.J.D. (1982). Inhibition of mouse sperm capacitation by ethanol. *Biol. Reprod.* **27**, 833-840.

Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. John Wiley and Sons, New York.

Arslanian, M.J., Pascoe, E., and Reinhold, J.G. (1971). Rat liver alcohol dehydrogenase: Purification and properties. *Biochem. J.* **125**, 1039-1047.

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity, and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* **257**, 229-306.

Baetcke, K.P., Hard, G.C., Rodgers, I.S., McGaughy, R.E., and Tahan, L.M. (1991). Alpha$_{2u}$-globulin: Association with chemically induced renal toxicity and neoplasia in the male rat. (EPA/625/3-91/019) Risk Assessment Forum, U.S. Environmental Protection Agency (USEPA) Washington, D.C.

Baker, R.C., Sorensen, S.M., and Deitrich, R.A. (1982). The in vivo metabolism of tertiary butanol by adult rats. *Alcohol: Clin. Exp. Res.* **6**, 247-251.

Beaugé, F., Clément, M., Nordmann, J., and Nordmann, R. (1981). Liver lipid disposal following *t*-butanol administration to rats. *Chem.-Biol. Interact.* **38**, 45-51.

Bechtel, D.H., and Cornish, H.H. (1972). Effect of the butyl alcohols on liver microsomal enzymes. *Toxicol. Appl. Pharmacol.* **22**, 298-299. (Abstr.)

Bellin, S.I., and Edmonds, H.L., Jr. (1976). The use of tert-butanol in alcohol dependence studies. *Proc. West. Pharmacol. Soc.* **19**, 351-354.

Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.

Caspary, W.J., Lee, Y.J., Poulton, S., Myhr, B.C., Mitchell, A.D., and Rudd, C.J. (1988). Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Quality control guidelines and response categories. *Environ. Mol. Mutagen.* **12** (Suppl. 13), 19-36.

Cederbaum, A.I., and Cohen, G. (1980). Oxidative demethylation of t-butyl alcohol by rat liver microsomes. *Biochem. Biophys. Res. Commun.* **97**, 730-736.

Cederbaum, A.I., Qureshi, A., and Cohen, G. (1983). Production of fomaldehyde and acetone by hydroxyl-radical generating systems during the metabolism of tertiary butyl alcohol. *Biochem. Pharmacol.* **32**, 3517-3524.

Chapin, R.E., Breese, G.R., and Mueller, R.A. (1980). Possible mechanisms of reduction of plasma luteinizing hormone by ethanol. *J. Pharmacol. Exp. Ther.* **212**, 6-10.

Charbonneau, M., Short, B.G., Lock, E.A., and Swenberg, J.A. (1987). Mechanism of petroleum-induced sex-specific protein droplet nephropathy and renal cell proliferation in Fischer-344 rats: Relevance to humans. In *Trace Substances in Environmental Health* (D.D. Hemphill, Ed.), Vol. 21, pp. 263-273. University of Missouri, Columbia, MO.

Charbonneau, M., Strasser, J., Lock, E.A., Turner, M.J., and Swenberg, J.A. (1989). 1,4-Dichlorobenzene-induced nephrotoxicity: Similarity with unleaded gasoline (UG)-induced renal effects. In *Nephrotoxicity: In Vitro to In Vivo, Animals to Man* (P.H. Bach and E.A. Lock, Eds.), pp. 557-562. Plenum Press, New York.

Chemical Economics Handbook (1993). *Gasoline Octane Improvers*. SRI International, Menlo Park, CA. December 1993 online update.

Code of Federal Regulations (CFR) **21**, Part 58.

Code of Federal Regulations (CFR) **21**, § 176.200.

Code of Federal Regulations (CFR) **21**, § 178.3910.

Code of Federal Regulations (CFR) **29**, § 1910.1000.

Coleman, W.E., Lingg, R.D., Melton, R.G., and Kopfler, F.C. (1976). The occurrence of volatile organics in five drinking water supplies using gas chromatography/mass spectrometry. In *Analysis and Identification of Organic Substances in Water* (L.H. Keith, Ed.), pp. 305-327. Ann Harbor Scientific Publishers, Inc., Ann Arbor, MI.

Cosmetic Ingredient Review Expert Panel (1989). Final report on the safety assessment of *t*-butyl alcohol. *J. Am. Coll. Toxicol.* **8**, 627-641.

Cox, D.R. (1972). Regression models and life-tables. *J. R. Stat. Soc.* **B34**, 187-220.

Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology: Mechanisms and Toxicity of Chemical Carcinogens and Mutagens* (M.A. Mehlman, W.G. Flamm, and R.J. Lorentzen, Eds.), pp. 13-59. Princeton Scientific Publishing Co. Inc., Princeton, NJ.

Daniel, M.A., and Evans, M.A. (1982). Quantitative comparison of maternal ethanol and maternal tertiary butanol diet on postnatal development. *J. Pharmacol. Exp. Ther.* **222**, 294-300.

Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* **6**, 44-52.

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* **32**, 236-248.

Dowty, B.J., Carlisle, D.R., and Laseter, J.L. (1975). New Orleans drinking water sources tested by gas chromatography-mass spectrometry. *Environ. Sci. Technol.* **9**, 762-765.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* **6**, 241-252.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50**, 1096-1121.

Edwards, E.K., Jr., and Edwards, E.K. (1982). Allergic reaction to tertiary butyl alcohol in a sunscreen. *Cutis* **29**, 476-478.

Eustis, S.L., Hailey, J.R., Boorman, G.A., and Haseman, J.K. (1994). The utility of multiple-section sampling in the histopathological evaluation of the kidney for carcinogenicity studies. *Toxicol. Pathol.* **22**, 457-472.

Faulkner, T.P., Wiechart, J.D., Hartman, D.M., and Hussain, A.S. (1989). The effects of prenatal tertiary butanol administration in CBA/J and C57BL/6J mice. *Life Sci.* **45**, 1989-1995.

Federal Register (1979). Waiver application by Atlantic Richfield Co., decision of the Administrator. Vol. 44, No. 36, pp. 10530-10542. U.S. Environmental Protection Agency, Washington, D.C.

Galloway, S.M., Bloom, A.D., Resnick, M., Margolin, B.H., Nakamura, F., Archer, P., and Zeiger, E. (1985). Development of a standard protocol for *in vitro* cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. *Environ. Mutagen.* **7**, 1-51.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environ. Mol. Mutagen.* **10** (Suppl. 10), 1-175.

Gart, J.J., Chu, K.C., and Tarone, R.E. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *J. Natl. Cancer Inst.* **62**, 957-974.

Grant, K.A., and Samson, H.H. (1982). Ethanol and tertiary butanol induced microcephaly in the neonatal rat: Comparison of brain growth parameters. *Neurobehav. Toxicol. Teratol.* **4**, 315-321.

Hard, G.C. (1986). Experimental models for the sequential analysis of chemically-induced renal carcinogenesis. *Toxicol. Pathol.* **14**, 112-122.

Harris, R.N., and Anders, M.W. (1980). Effect of fasting, diethyl maleate, and alcohols on carbon tetrachloride-induced hepatotoxicity. *Toxicol. Appl. Pharmacol.* **56**, 191-198.

Haseman, J.K. (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. *Environ. Health Perspect.* **58**, 385-392.

Haseman, J.K. (1992). Value of historical controls in the interpretation of rodent tumor data. *Drug Inf. J.* **26**, 191-200.

Haseman, J.K., and Rao, G.N. (1992). Effects of corn oil, time-related changes, and inter-laboratory variability on tumor occurrence in control Fischer 344 (F344/N) rats. *Toxicol. Pathol.* **20**, 52-60.

Haseman, J.K., Huff, J., and Boorman, G.A. (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol. Pathol.* **12**, 126-135.

Haseman, J.K., Huff, J.E., Rao, G.N., Arnold, J.E., Boorman, G.A., and McConnell, E.E. (1985). Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. *JNCI* **75**, 975-984.

Haseman, J.K., Bourbina, J., and Eustis, S.L. (1994). The effect of individual housing and other experimental design factors on tumor incidence in B6C3F_1 mice. *Fundam. Appl. Toxicol.* **23**, 44-52.

Hawley, G.G., Ed. (1981). *The Condensed Chemical Dictionary*, 10th ed., p. 161. Van Nostrand Reinhold Co., New York.

Hill, R.N., Erdreich, L.S., Paynter, O.E., Roberts, P.A., Rosenthal, S.L., and Wilkinson, C.F. (1989). Thyroid follicular cell carcinogenesis. *Fundam. Appl. Toxicol.* **12**, 629-697.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*, pp. 120-123. John Wiley and Sons, New York.

Hoshino, H., Chihara, G., and Fukuoka, F. (1970). Detection of potential weak carcinogens and procarcinogens. II. Carcinogenicity of tertiary butyl hydroperoxide. *Gann* **61**, 121-124.

Jonckheere, A.R. (1954). A distribution-free *k*-sample test against ordered alternatives. *Biometrika* **41**, 133-145.

Kamil, I.A., Smith, J.N., and Williams, R.T. (1953). The metabolism of aliphatic alcohols. The glucuronic acid conjugation of acyclic aliphatic alcohols. *J. Biochem.* **53**, 129-136.

Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**, 457-481.

Lafleur, M.V.M., and Loman, H. (1982). Influence of anoxic sensitizers on the radiation damage in biologically active DNA in aqueous solution. *Int. J. Radiat. Biol.* **41**, 295-302.

LeBlanc, A.E., and Kalant, H. (1975). Ethanol-induced cross tolerance to several homologous alcohols in the rat. *Toxicol. Appl. Pharmacol.* **32**, 123-128.

Lock, E.A., Charbonneau, M., Strasser, J., Swenberg, J.A., and Bus, J.S. (1987). 2,2,4-Trimethylpentane-induced nephrotoxicity. II. The reversible binding of a TMP metabolite to a renal protein fraction containing α_{2u}-globulin. *Toxicol. Appl. Pharmacol.* **91**, 182-192.

McClain, R.M. (1989). The significance of hepatic microsomal enzyme induction and altered thyroid function in rats: Implications for thyroid gland neoplasia. *Toxicol. Pathol.* **17**, 294-306.

McComb, J.A., and Goldstein, D.B. (1979). Quantitative comparison of physical dependence on tertiary butanol and ethanol in mice: Correlation with lipid solubility. *J. Pharmacol. Exp. Ther.* **208**, 113-117.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **78**, 283-289.

McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D., and Caspary, W.J. (1988). Responses of the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay. II. 18 coded chemicals. *Environ. Mol. Mutagen.* **11**, 91-118.

MacGregor, J.T., Wehr, C.M., and Langlois, R.G. (1983). A simple fluorescent staining procedure for micronuclei and RNA in erythrocytes using Hoechst 33258 and pyronin Y. *Mutat. Res.* **120**, 269-275.

MacGregor, J.T., Wehr, C.M., Henika, P.R., and Shelby, M.D. (1990). The *in vivo* erythrocyte micronucleus test: Measurement at steady state increases assay efficiency and permits integration with toxicity studies. *Fundam. Appl. Toxicol.* **14**, 513-522.

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* **79**, 639-648.

Maickel, R.P., and McFadden, D.P. (1979). Acute toxicology of butyl nitrites and butyl alcohols. *Res. Commun. Chem. Pathol. Pharmacol.* **26**, 75-83.

Maronpot, R.R., and Boorman, G.A. (1982). Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. *Toxicol. Pathol.* **10**, 71-80.

The Merck Index (1983). 10th ed. (M. Windholz, Ed.), p. 215. Merck and Company, Rahway, NJ.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), pp. 605-627. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Morrison, D.F. (1976). *Multivariate Statistical Methods*, 2nd ed., pp. 170-179. McGraw-Hill Book Company, New York.

Munch, J.C. (1972). Aliphatic alcohols and alkyl esters: Narcotic and lethal potencies to tadpoles and to rabbits. *Ind. Med.* **41**, 31-33.

National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Institutes of Health (NIH) (1978). Open Formula Mouse and Rat Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Institute for Occupational Safety and Health (NIOSH) (1994). National Occupational Exposure Survey (NOES) (1981-1983), unpublished provisional data as of January 31, 1994.

National Toxicology Program (NTP) (1984). Technical Protocol for Sperm Morphology and Vaginal Cytology Evaluations in Toxicity Testing for Rats and Mice, 10/31/82 version (updated April 1984). Research Triangle Park, NC.

National Toxicology Program (NTP) (1987). Toxicology and Carcinogenesis Studies of 1,4-Dichlorobenzene (CAS No. 106-46-7) in F344/N Rats and $B6C3F_1$ Mice (Gavage Studies). Technical Report Series No. 319. NIH Publication No. 87-2575. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Trangle Park, NC.

National Toxicology Program (NTP) (1989). Toxicology and Carcinogenesis Studies of Hexachloroethane (CAS No. 67-72-1) in F344/N Rats (Gavage Studies). Technical Report Series 361. NIH Publication No. 89-2816. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Trangle Park, NC.

National Toxicology Program (NTP) (1990). Toxicology and Carcinogenesis Studies of *d*-Limonene (CAS No. 5989-27-5) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 347. NIH Publication No. 90-2802. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Trangle Park, NC.

Nelson, B.K., Brightwell, W.S., Khan., A., Burg, J.R., and Goad, P.T. (1989). Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats. *Fundam. Appl. Toxicol.* **12**, 469-479.

Nelson, B.K., Brightwell, W.S., Khan, A., Shaw, P.B., Krieg, E.F., Jr., and Massari, V.J. (1991). Behavioral teratology investigation of tertiary-butanol administered by inhalation to rats. *Pharmacopsychoecologia* **4**, 1-7.

Patty's Industrial Hygiene and Toxicology (1982). 3rd ed. (G.D. Clayton and F.E. Clayton, Eds.), Vol. 2C, pp. 4585-4588. John Wiley and Sons, New York.

Pellizzari, E.D., Hartwell, T.D., Harris, B.S.H., III, Waddell, R.D., Whitaker, D.A., and Erickson, M.D. (1982). Purgeable organic compounds in mother's milk. *Bull. Environ. Contam. Toxicol.* **28**, 322-328.

Peter, C.P., Burek, J.D., and van Zwieten, M.J. (1986). Spontaneous nephropathies in rats. *Toxicol. Pathol.* **14**, 91-100.

Roots, R., and Okada, S. (1972). Protection of DNA molecules of cultured mammalian cells from radiation-induced single-strand scissions by various alcohols and SH compounds. *Int. J. Radiat. Biol.* **21**, 329-342.

Sadtler Standard Spectra. IR No. 2; NMR No. 10198M. Sadtler Research Laboratories, Philadelphia, PA.

Schaffarzick, R.W., and Brown, B.J. (1952). The anticonvulsant activity and toxicity of methylparafynol (Dormison®) and some other alcohols. *Science* **116**, 663-665.

Schmid, W. (1976). The micronucleus test for cytogenetic analysis. In *Chemical Mutagens: Principles and Methods for their Detection* (A. Hollaender, Ed.), Vol. 4, pp. 31-53. Plenum Press, New York.

Sexton, K., Webber, L.M., and Hayward, S.B. (1986). Characterization of particle composition, organic vapor constituents, and mutagenicity of indoor air pollutant emissions. *Environ. Int.* **12**, 351-362.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* **33**, 386-389.

Snell, D., and Harris, R.A. (1980). Impairment of avoidance behavior following short-term ingestion of ethanol, tertiary-butanol, or phenobarbitol in mice. *Psychopharmacology* **69**, 53-57.

Stonard, M.D., Phillips, P.G.N., Foster, J.R., Simpson, M.G., and Lock, E.A. (1986). α_{2u}-Globulin: Measurement in rat kidney following administration of 2,2,4-trimethylpentane. *Toxicology* **41**, 161-168.

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* **67**, 233-241.

Takahashi, K., Lindamood, C., III, and Maronpot, R.R. (1993). Retrospective study of possible α-2μ-globulin nephropathy and associated cell proliferation in male Fischer 344 rats dosed with *t*-butyl alcohol. *Environ. Health Perspect.* **101** (Suppl. 5), 281-286.

Tarone, R.E. (1975). Tests for trend in life table analysis. *Biometrika* **62**, 679-682.

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* **236**, 933-941.

Thore, A., and Baltscheffsky, H. (1965). Inhibitory effects of lower aliphatic alcohols on electron transport phosphorylation systems. 2. Secondary, tertiary, and di-alcohols. *Acta Chem. Scand.* **19**, 1600-1606.

Thurman, R.G., and Pathman, D.E. (1975). Withdrawal symptoms from ethanol: Evidence against the involvement of acetaldehyde. In *The Role of Acetaldehyde in the Actions of Ethanol, 6th Int. Congr. Pharmacol.* (K.O. Lindros and C.J.P. Erikkson, Eds.), Vol. 23, pp. 217-231. The Finnish Foundation for Alcohol Studies, Helsinki.

Thurman, R.G., Winn, K., and Urquhart, B. (1980). Rat brain cyclic AMP levels and withdrawal behavior following treatment with t-butanol. *Adv. Exp. Med. Biol.* **126**, 271-281.

Videla, L.A., Fernández, V., and de Marinis, A. (1982). Liver lipoperoxidative pressure and glutathione status following acetaldehyde and aliphatic alcohols pretreatments in the rat. *Biochem. Biophys. Res. Commun.* **104**, 965-970.

Wallgren, H. (1960). Relative intoxicating effects on rats of ethyl, propyl and butyl alcohols. *Acta Pharmacol. Toxicol.* **16**, 217-222.

West, R.W., Frith, C.H., Stanley, J.W., and Jackson, C.D. (1984). The role of urinary physiological changes in the genesis of urothelial lesions in mice given 4-ethyl-sulfonylnaphthalene-1-sulfonamide, acetazolamide, and oxamide. *J. Environ. Pathol. Toxicol. Oncol.* **5**, 39-50.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* **28**, 519-531.

Williams, R.T. (1959). *Detoxication Mechanisms: The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds*, 2nd ed., pp. 67-68. John Wiley and Sons, New York.

Wood, J.M., and Laverty, R. (1979). Physical dependence following prolonged ethanol or *t*-butanol administration to rats. *Pharmacol. Biochem. Behav.* **10**, 113-119.

Yojay, L., Yojay, R., and Mardones, J. (1982). Acetone blood levels after t-butanol administration in rats. *IRCS Med. Sci.* **10**, 215.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., and Speck, W. (1987). *Salmonella* mutagenicity tests. III. Results from the testing of 255 chemicals. *Environ. Mutagen.* **9** (Suppl. 9), 1-110.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four in vitro genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16** (Suppl. 18), 1-14.

APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *t*-BUTYL ALCOHOL

TABLE A1 Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 67

TABLE A2 Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 72

TABLE A3 Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 94

TABLE A4 Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats 100

TABLE A5 Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 101

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	31	35	41	46
Natural deaths	9	9	5	3
Survivors				
Terminal sacrifice	10	6	4	1
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Endocrine System				
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, adenoma	6 (60%)	5 (50%)	4 (40%)	4 (44%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, adenoma	1 (10%)	1 (10%)		1 (10%)
Genital System				
Testes	(10)	(10)	(10)	(10)
Bilateral, interstitial cell, adenoma	2 (20%)	3 (30%)	6 (60%)	4 (40%)
Interstitial cell, adenoma	2 (20%)		2 (20%)	3 (30%)
Hematopoietic System				
Lymph node, mandibular	(10)	(10)	(10)	(10)
Spleen	(10)	(10)	(10)	(10)
Thymus	(9)	(10)	(9)	(9)
Thymoma benign				1 (11%)
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Squamous cell papilloma			1 (10%)	
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia mononuclear				2 (20%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(49)	(50)	(50)
Intestine large, rectum	(49)	(48)	(49)	(50)
Histiocytic sarcoma, metastatic, liver				1 (2%)
Intestine large, cecum	(50)	(49)	(50)	(50)
Intestine small, duodenum	(48)	(43)	(46)	(50)
Intestine small, jejunum	(50)	(47)	(50)	(50)
Intestine small, ileum	(50)	(48)	(49)	(50)
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic			1 (2%)	1 (2%)
Carcinoma, metastatic, thyroid gland	1 (2%)			
Fibrosarcoma, metastatic, skin				1 (2%)
Hepatocellular adenoma	1 (2%)	1 (2%)		
Histiocytic sarcoma				1 (2%)
Mesentery	(5)	(6)	(9)	(3)
Carcinoma, metastatic, pancreas			1 (11%)	
Fibrosarcoma, metastatic, skin				1 (33%)
Hemangiosarcoma			1 (11%)	
Pancreas	(50)	(49)	(50)	(50)
Carcinoma		1 (2%)	1 (2%)	
Acinar cell, adenoma	3 (6%)	6 (12%)	1 (2%)	1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma				1 (2%)
Stomach, glandular	(50)	(49)	(50)	(50)
Tongue	(1)			(1)
Squamous cell papilloma	1 (100%)			1 (100%)
Tooth				(1)
Fibrosarcoma				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic			1 (2%)	
Schwannoma benign	1 (2%)			
Thymoma malignant, metastatic, thymus				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Carcinoma, metastatic, pancreas			1 (2%)	
Carcinoma, metastatic, thyroid gland	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal medulla	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland	1 (2%)			
Ganglioneuroma			1 (2%)	
Pheochromocytoma malignant	4 (8%)	1 (2%)	2 (4%)	
Pheochromocytoma benign	9 (18%)	6 (12%)	4 (8%)	4 (8%)
Bilateral, pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(50)	(49)	(49)	(49)
Adenoma	15 (30%)	15 (31%)	7 (14%)	6 (12%)
Carcinoma	2 (4%)		2 (4%)	
Histiocytic sarcoma, metastatic, liver				1 (2%)
Pituitary gland	(49)	(50)	(49)	(49)
Pars distalis, adenoma	33 (67%)	33 (66%)	31 (63%)	23 (47%)
Pars distalis, carcinoma	1 (2%)			
Pars intermedia, adenoma			1 (2%)	
Thyroid gland	(50)	(49)	(50)	(50)
C-cell, adenoma	4 (8%)	4 (8%)	1 (2%)	4 (8%)
C-cell, carcinoma	1 (2%)	2 (4%)		1 (2%)
Follicular cell, adenoma	2 (4%)			
Follicular cell, carcinoma	2 (4%)			
General Body System				
Tissue NOS			(1)	(2)
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic, liver				1 (2%)
Preputial gland	(50)	(50)	(50)	(49)
Adenoma	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Carcinoma	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Carcinoma, metastatic, thyroid gland				1 (2%)
Prostate	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	21 (42%)	14 (28%)	13 (26%)	20 (40%)
Interstitial cell, adenoma	13 (26%)	17 (34%)	18 (36%)	13 (26%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(19)	(11)	(14)	(19)
Mediastinal, carcinoma, metastatic, pancreas			1 (7%)	
Pancreatic, carcinoma, metastatic, islets, pancreatic			1 (7%)	
Lymph node, mandibular	(50)	(48)	(49)	(50)
Lymph node, mesenteric	(49)	(49)	(50)	(50)
Spleen	(50)	(49)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic			1 (2%)	
Thymus	(45)	(49)	(48)	(47)
Thymoma benign	1 (2%)			1 (2%)
Thymoma malignant		1 (2%)		1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
2-Year Study (continued)				
Integumentary System				
Mammary gland	(44)	(50)	(47)	(47)
Fibroadenoma	1 (2%)	2 (4%)	1 (2%)	
Skin	(50)	(50)	(49)	(50)
Basal cell adenoma			2 (4%)	
Carcinoma, metastatic, islets, pancreatic			1 (2%)	
Keratoacanthoma		2 (4%)	2 (4%)	1 (2%)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma	3 (6%)	3 (6%)	1 (2%)	1 (2%)
Sebaceous gland, adenoma			1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Chordoma	1 (2%)			
Skeletal muscle	(1)	(1)	(1)	
Carcinoma, metastatic, pancreas			1 (100%)	
Chordoma, metastatic, bone	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Oligodendroglioma benign				1 (2%)
Spinal cord	(1)	(1)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)	
Alveolar/bronchiolar carcinoma				1 (2%)
Carcinoma, metastatic, islets, pancreatic			1 (2%)	
Carcinoma, metastatic, pancreas			1 (2%)	
Carcinoma, metastatic, preputial gland			1 (2%)	
Carcinoma, metastatic, thyroid gland	1 (2%)	1 (2%)		1 (2%)
Chordoma, metastatic, bone	1 (2%)			
Squamous cell carcinoma		1 (2%)		
Thymoma malignant, metastatic, thymus				1 (2%)
Nose	(50)	(50)	(50)	(50)
Special Senses System				
Zymbal's gland			(1)	(1)
Carcinoma			1 (100%)	1 (100%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Bilateral, renal tubule, adenoma, multiple				1 (2%)
Renal tubule, adenoma	1 (2%)	3 (6%)	4 (8%)	2 (4%)
Renal tubule, carcinoma				1 (2%)
Renal tubule, oncocytoma benign	1 (2%)			
Transitional epithelium, papilloma			1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic, liver				1 (2%)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	30 (60%)	28 (56%)	24 (48%)	23 (46%)
Lymphoma malignant mixed			1 (2%)	
Mesothelioma benign			1 (2%)	
Mesothelioma malignant		1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	10	8	9	9
2-Year study	49	49	50	50
Total primary neoplasms				
15-Month interim evaluation	11	9	13	15
2-Year study	159	150	130	116
Total animals with benign neoplasms				
15-Month interim evaluation	10	8	9	9
2-Year study	47	47	49	47
Total benign neoplasms				
15-Month interim evaluation	11	9	13	13
2-Year study	115	111	93	83
Total animals with malignant neoplasms				
15-Month interim evaluation				2
2-Year study	38	33	32	28
Total malignant neoplasms				
15-Month interim evaluation				2
2-Year study	44	39	37	33
Total animals with metastatic neoplasms				
2-Year study	2	1	3	4
Total metastatic neoplasms				
2-Year study	6	1	12	11

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL

Number of Days on Study	0	2	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6
	2	8	0	2	2	5	5	5	5	6	6	7	7	8	8	8	9	9	9	0	0	1	1	1	2
	0	8	5	6	6	3	3	3	3	2	3	2	3	6	8	9	4	4	5	3	4	4	7	7	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	2	2	3	0	1	3	4	2	4	2	4	1	0	2	0	1	0	1	3	5	1	5	5
	1	3	5	9	9	2	6	0	9	6	8	3	0	2	5	2	1	8	8	0	4	8	1	7	4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																				X					
Hepatocellular adenoma						X																			
Mesentery			+													+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel																+								+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma, metastatic, thyroid gland																				X					
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																				X					
Pheochromocytoma malignant															X							X			
Pheochromocytoma benign															X				X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				X
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X		X	X	X	X		X		X	X	X	X		X				X			X
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																				X					
Follicular cell, adenoma													X								X				
Follicular cell, carcinoma																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	623	630	636	637	645	646	657	669	672	678	692	694	698	720	720	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	019	031	050	059	007	027	046	021	041	045	037	004	043	032	055	006	013	015	020	028	035	036	044	053	060	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Hepatocellular adenoma																										1
Mesentery	+												+					+								5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell, adenoma												X	X								X					3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																								+		1
Squamous cell papilloma																								X		1
Cardiovascular System																										
Blood vessel			+			+		+													+					6
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign												X														1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Carcinoma, metastatic, thyroid gland																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Pheochromocytoma malignant																								X	X	4
Pheochromocytoma benign		X					X			X	X		X			X		X								9
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X		X	X	X		X			X	X	X	X			X	X				X		X		15
Carcinoma			X																X							2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Pars distalis, adenoma		X	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X			33
Pars distalis, carcinoma					X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X														X	X			X					4
C-cell, carcinoma																										1
Follicular cell, adenoma																										2
Follicular cell, carcinoma	X			X																						2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	0	2	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6
	2	8	0	2	2	5	5	5	5	6	6	7	7	8	8	8	9	9	9	0	0	1	1	1	2
	0	8	5	6	6	3	3	3	3	2	3	2	3	6	8	9	4	4	5	3	4	4	7	7	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	2	2	3	0	1	3	4	2	4	2	4	1	0	2	0	1	0	1	3	5	1	5	5
	1	3	5	9	9	2	6	0	9	6	8	3	0	2	5	2	1	8	8	0	4	8	1	7	4
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma							X																		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X				X			X					X		X				X	X	
Interstitial cell, adenoma			X			X					X				X	X		X		X		X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+	+						+		+	+		+	+			+		+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	M	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	I	+	M	+	+	+	M	+	+	+	+	M	+	+	M
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X									X	
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma																									
Skeletal muscle																									
Chordoma, metastatic, bone																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord		+																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, thyroid gland																				X					
Chordoma, metastatic, bone																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	623	630	636	637	645	646	657	669	672	678	692	694	698	720	720	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	019	031	050	059	007	027	046	021	041	045	037	044	043	032	055	061	013	015	020	028	035	036	044	053	060	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																				X			2
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X				X		X		X	X				X		X		X	X	X		X	X	X	X	21
Interstitial cell, adenoma				X		X					X	X					X									13
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+		+					+	+				+	+		+			+						19
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	45
Thymoma benign																		X								1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Fibroadenoma														X												1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma															X											3
Subcutaneous tissue, fibroma											X															1
Subcutaneous tissue, fibrosarcoma												X														2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma																						X				1
Skeletal muscle																						+				1
Chordoma, metastatic, bone																						X				1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										1
Carcinoma, metastatic, thyroid gland																										1
Chordoma, metastatic, bone																						X				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	0	2	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6
	2	8	0	2	2	5	5	5	5	6	6	7	7	8	8	8	9	9	9	0	0	1	1	1	2
	0	8	5	6	6	3	3	3	3	2	3	2	3	6	8	9	4	4	5	3	4	4	7	7	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	2	2	3	0	1	3	4	2	4	2	4	1	0	2	0	1	0	1	3	5	1	5	5
	1	3	5	9	9	2	6	0	9	6	8	3	0	2	5	2	1	8	8	0	4	8	1	7	4
Special Senses System																										
Eye																+	+									
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																										
Renal tubule, oncocytoma benign																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X	X	X		X	X	X	X		X			X	X			X		X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	623	630	636	637	645	646	657	669	672	678	692	694	698	720	720	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	019	031	050	059	007	027	046	021	041	045	037	044	043	032	055	006	013	015	020	028	035	036	044	053	060	Total Tissues/ Tumors
Special Senses System																										
Eye																		+				+				4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																		X								1
Renal tubule, oncocytoma benign																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X			X		X	X	X	X	X	X			X			X	X		X	X	X	30

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 1.25 mg/mL

Number of Days on Study	307	348	395	512	520	553	557	562	569	575	577	585	584	591	596	602	603	603	605	619	624	624	626	629	630
Carcass ID Number	074	084	101	099	068	072	075	113	114	067	073	085	161	065	093	094	076	091	105	095	087	121	089	069	110
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																				X					
Mesentery						+								+											
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Acinar cell, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																						X			
Pheochromocytoma benign																						X			
Bilateral, pheochromocytoma benign													X												
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X									X				X					X		X
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X	X	X	X	X	X	X		X				X		X	X		X	X	X		X
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X						X								
C-cell, carcinoma																								X	X
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																				+					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma		X												X	X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma										X			X	X			X		X	X					
Interstitial cell, adenoma				X		X	X				X				X	X							X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 1.25 mg/mL
(continued)

Number of Days on Study	639	646	651	651	656	666	666	672	673	679	679	692	693	694	699	708	708	720	720	731	731	731	731	731	731	
Carcass ID Number	0086	0062	0070	0097	1015	0083	1019	1012	0061	0066	0090	0100	0092	1017	0082	0079	0106	0096	1008	0063	0067	0080	0081	0098	1020	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	A	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery		+					+							+										+		6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma	X																									1
Acinar cell, adenoma													X		X			X			X	X	X			6
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel				+											+									+		3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign	X						X				X		X					X								6
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X	X		X	X	X				X	X	X		X					X		15
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma						X	X	X	X	X	X	X	X		X	X	X		X	X	X		X	X	X	33
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																				X		X				4
C-cell, carcinoma																										2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis									+																	2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X			X		X		X					X						X	X		X			14
Interstitial cell, adenoma			X	X							X	X			X			X	X			X		X	X	17

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 1.25 mg/mL
(continued)

Number of Days on Study	307	348	395	512	520	553	557	562	569	575	577	575	584	591	596	602	603	603	605	619	624	624	626	629	630
Carcass ID Number	074	084	101	109	068	072	075	113	114	067	073	085	016	065	093	094	076	091	095	095	087	012	089	069	110
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+			+	+							+	+	+	+				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X		
Squamous cell papilloma														X							X				
Subcutaneous tissue, fibroma													X				X								
Subcutaneous tissue, fibrosarcoma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																								X	
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																					+				
Eye																						+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X	X	X		X	X			X	X	X	X	X	X	X		
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 1.25 mg/mL
(continued)

Number of Days on Study	639	646	651	651	656	666	666	672	773	779	799	792	793	794	799	708	708	720	720	731	731	731	731	731	731	
Carcass ID Number	0086	0062	0070	0097	1015	0083	1019	1022	0061	0066	0090	0100	0092	1017	0082	0079	0106	0966	1008	0063	0078	0080	0081	0098	1020	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+	+																						11
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	49
Thymoma malignant									X																	1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																X									X	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																					X					2
Squamous cell papilloma																	X									3
Subcutaneous tissue, fibroma																			X							3
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+																									1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+																									1
Spinal cord	+																									1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Squamous cell carcinoma							X																			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear	+																									2
Eye													+													2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																	X							X	X	3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X		X		X	X	X	X				X	X	X		X		X	X				X	28
Mesothelioma malignant							X																			1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 2.5 mg/mL

Number of Days on Study	343	355	398	449	484	510	512	525	528	542	545	547	551	553	556	569	577	580	582	589	589	595	595	603	605
Carcass ID Number	129	145	141	178	152	166	160	137	123	168	161	133	139	126	130	125	169	136	146	143	149	156	163	122	134
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic										X															
Mesentery		+				+					+		+		+				+						
Carcinoma, metastatic, pancreas													X												
Hemangiosarcoma		X																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma													X												
Acinar cell, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic										X															
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas													X												
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganglioneuroma																		X							
Pheochromocytoma malignant							X																		
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X			X					X		
Carcinoma										X															
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pars distalis, adenoma			X	X		X	X		X			X		X	X	X		X	X	X	X	X			
Pars intermedia, adenoma	X																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
Tissue NOS																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 2.5 mg/mL
(continued)

Number of Days on Study	607	623	624	630	637	639	637	638	643	643	645	650	651	653	666	673	673	678	679	685	703	730	730	730	730	
Carcass ID Number	128	127	151	172	148	159	170	176	155	162	140	164	147	157	179	131	175	180	124	154	147	142	153	165	171	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+		+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																										1
Mesentery									+	+									+							9
Carcinoma, metastatic, pancreas																										1
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Acinar cell, adenoma																				X						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																							+			1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ganglioneuroma																										1
Pheochromocytoma malignant																							X			2
Pheochromocytoma benign					X					X												X		X		4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X				X		X			X				7
Carcinoma	X																									2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X			X	X			X	X	X		X		X	X	X	X	X	X	X	X	X	31
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X																					1
General Body System																										
Tissue NOS																									+	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 2.5 mg/mL
(continued)

Number of Days on Study	343	355	398	449	484	510	512	525	228	542	545	547	551	553	556	569	577	580	582	589	589	595	595	603	605
Carcass ID Number	129	145	141	178	152	166	160	137	123	168	161	133	139	126	130	125	169	136	146	143	149	156	163	122	134
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																				+					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma																				X					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X			X									X					X	X		X
Interstitial cell, adenoma										X	X		X		X									X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+					+	+		+							+			+		
Mediastinal, carcinoma, metastatic, pancreas													X												
Pancreatic, carcinoma, metastatic, islets, pancreatic										X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic										X															
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Fibroadenoma								X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Basal cell adenoma															X										
Carcinoma, metastatic, islets, pancreatic										X															
Keratoacanthoma																									
Squamous cell papilloma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma					X																				
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+												
Carcinoma, metastatic, pancreas													X												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 2.5 mg/mL
(continued)

Number of Days on Study	607	623	624	630	637	637	637	638	643	643	645	650	651	653	666	673	673	678	679	685	703	730	730	730	730	
Carcass ID Number	128	127	151	172	148	159	170	176	155	162	140	164	174	157	179	131	175	180	124	154	147	142	153	165	171	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma						X		X																		3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X			X					X				X				X		X					X	13
Interstitial cell, adenoma	X		X	X		X			X		X		X			X	X		X		X		X	X		18
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+				+		+			+		+				+					+		14
Mediastinal, carcinoma, metastatic, pancreas																										1
Pancreatic, carcinoma, metastatic, islets, pancreatic																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell adenoma			X																							2
Carcinoma, metastatic, islets, pancreatic																										1
Keratoacanthoma								X															X			2
Squamous cell papilloma																		X								1
Sebaceous gland, adenoma																	X									1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma		X																								1
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Carcinoma, metastatic, pancreas																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 2.5 mg/mL
(continued)

Number of Days on Study	343	355	398	449	484	510	512	525	528	542	545	547	551	553	556	569	577	580	582	589	589	595	595	603	605
Carcass ID Number	129	145	141	178	152	166	160	137	123	168	161	133	139	126	130	125	169	136	146	143	149	156	163	122	134
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, islets, pancreatic										X															
Carcinoma, metastatic, pancreas													X												
Carcinoma, metastatic, preputial gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye						+																			
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									X
Transitional epithelium, papilloma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X			X				X	X				X			X	X	
Lymphoma malignant mixed				X																					
Mesothelioma benign																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 2.5 mg/mL
(continued)

Number of Days on Study	607	623	624	630	637	637	637	638	643	643	645	650	651	653	666	673	673	678	679	685	703	730	730	730	730	
Carcass ID Number	128	127	151	172	148	159	170	176	155	162	140	164	174	157	179	131	175	180	124	154	147	142	153	165	171	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				1
Carcinoma, metastatic, islets, pancreatic																										1
Carcinoma, metastatic, pancreas																										1
Carcinoma, metastatic, preputial gland						X																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear		+																								1
Eye																+										2
Zymbal's gland		+																								1
Carcinoma		X																								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma													X	X							X					4
Transitional epithelium, papilloma																		X								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X		X	X		X	X		X			X	X	X		X		X		X	X	X	X	X	24
Lymphoma malignant mixed																										1
Mesothelioma benign									X																	1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL

Number of Days on Study	262	274	506	508	526	553	555	555	562	566	569	569	575	575	575	577	583	587	588	589	594	594	594	594	595
Carcass ID Number	207	214	209	198	184	191	186	230	221	231	225	234	192	193	237	181	224	196	195	232	197	202	203	215	183
Alimentary System																									
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, liver																									
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic																									
Fibrosarcoma, metastatic, skin										X															
Histiocytic sarcoma																									
Mesentery										+		+								+					
Fibrosarcoma, metastatic, skin										X															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma															X										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																							+		
Squamous cell papilloma																							X		
Tooth												+													
Fibrosarcoma												X													
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant, metastatic, thymus		X																							
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign			X												X				X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																	X	
Histiocytic sarcoma, metastatic, liver																									
Parathyroid gland	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X						X	X	X	X	X	X						X	X				X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																						X			
C-cell, carcinoma							X																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	596	598	598	604	600	604	604	624	624	636	639	646	650	651	653	666	667	669	672	672	679	679	679	708	729	
Carcass ID Number	236	208	217	204	210	222	204	185	190	226	233	227	218	229	211	213	201	205	188	228	200	191	220	239	187	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, liver																	X									1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																	X									1
Fibrosarcoma, metastatic, skin																										1
Histiocytic sarcoma																	X									1
Mesentery																										3
Fibrosarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Tooth																										1
Fibrosarcoma																										1
Cardiovascular System																										
Blood vessel													+													1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymoma malignant, metastatic, thymus																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign												X														4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X					X	X					X										6
Histiocytic sarcoma, metastatic, liver																	X									1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X			X	X			X	X	X		X					X	X	X	X	X	X		23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X						X							X										4
C-cell, carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	2	2	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	6	7	0	0	2	5	5	5	6	6	6	6	7	7	7	7	8	8	8	8	9	9	9	9	9
	2	4	6	8	6	3	5	5	2	6	9	9	5	5	5	7	3	7	8	9	4	4	4	4	5
Carcass ID Number	2	2	2	1	1	1	1	2	2	2	2	2	1	1	2	1	2	1	1	2	1	2	2	2	1
	0	1	0	9	8	9	8	3	2	3	2	3	9	9	3	8	2	9	9	3	9	0	0	1	8
	7	4	9	8	4	1	6	0	1	1	5	4	2	3	7	1	4	6	5	2	7	2	3	5	3
General Body System																									
Tissue NOS												+							+						
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, liver																									
Preputial gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma	X																								
Carcinoma, metastatic, thyroid gland							X																		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X		X		X						X	X	X				X			
Interstitial cell, adenoma				X	X							X	X	X	X								X	X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+		+		+			+		+	+	+		+	+		+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Thymoma benign																									
Thymoma malignant		X																							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma								X																	
Squamous cell carcinoma																									
Squamous cell papilloma														X											
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma benign																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	596	598	598	604	604	604	604	624	624	636	639	646	650	651	653	666	667	669	672	672	679	679	679	708	729	
Carcass ID Number	236	208	107	204	101	222	204	185	190	226	233	227	218	229	211	113	101	205	188	228	201	191	220	239	187	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										2
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, liver																	X									1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									X	2
Carcinoma																										1
Carcinoma, metastatic, thyroid gland																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X		X	X				X		X	X	X			X	X		X			X			X	20
Interstitial cell, adenoma								X										X		X			X	X		13
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+						+			+	+			+		+			+						19
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymoma benign																									X	1
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Squamous cell carcinoma																			X							1
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma																							X			1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma benign																				X						1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	2	2	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	6	7	0	0	2	5	5	5	6	6	6	6	7	7	7	7	8	8	8	8	9	9	9	9	9
	2	4	6	8	6	3	5	5	2	6	9	9	5	5	5	7	3	7	8	9	4	4	4	4	5
Carcass ID Number	2	2	2	1	1	1	1	2	2	2	2	2	1	1	2	1	2	1	1	2	1	2	2	2	1
	0	1	0	9	8	9	8	3	2	3	2	3	9	9	3	8	2	9	9	3	9	0	0	1	8
	7	4	9	8	4	1	6	0	1	1	5	4	2	3	7	1	4	6	5	2	7	2	3	5	3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, thyroid gland							X																		
Thymoma malignant, metastatic, thymus		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland					+																				
Carcinoma					X																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, renal tubule, adenoma, multiple										X															
Renal tubule, adenoma																		X							
Renal tubule, carcinoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, liver																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear			X	X		X	X	X				X	X		X		X	X	X	X					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	596	598	598	604	604	604	604	624	624	636	639	646	650	651	653	666	667	669	672	672	679	679	679	708	729	
Carcass ID Number	236	208	217	204	210	222	240	185	190	226	233	227	218	229	211	113	101	205	188	228	200	191	220	239	187	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																		X								1
Carcinoma, metastatic, thyroid gland																										1
Thymoma malignant, metastatic, thymus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																		+		+						2
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, renal tubule, adenoma, multiple																										1
Renal tubule, adenoma																							X			2
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, liver																	X									1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																	X									1
Leukemia mononuclear								X		X	X	X		X	X	X	X	X		X			X			23

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	9/50 (18%)	7/50 (14%)	4/50 (8%)	4/50 (8%)
Adjusted rate[b]	44.7%	35.0%	55.2%	14.2%
Terminal rate[c]	2/10 (20%)	0/6 (0%)	2/4 (50%)	0/1 (0%)
First incidence (days)	588	584	637	506
Life table test[d]	P=0.545N	P=0.442N	P=0.446N	P=0.568N
Logistic regression test[d]	P=0.157N	P=0.384N	P=0.253N	P=0.173N
Cochran-Armitage test[d]	P=0.071N			
Fisher exact test[d]		P=0.393N	P=0.117N	P=0.117N
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	4/50 (8%)	1/50 (2%)	2/50 (4%)	0/50 (0%)
Adjusted rate	24.9%	3.3%	26.7%	0.0%
Terminal rate	2/10 (20%)	0/6 (0%)	1/4 (25%)	0/1 (0%)
First incidence (days)	588	624	512	–[e]
Life table test	P=0.182N	P=0.223N	P=0.586N	P=0.251N
Logistic regression test	P=0.070N	P=0.176N	P=0.414N	P=0.110N
Cochran-Armitage test	P=0.052N			
Fisher exact test		P=0.181N	P=0.339N	P=0.059N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	12/50 (24%)	7/50 (14%)	6/50 (12%)	4/50 (8%)
Adjusted rate	60.0%	35.0%	78.1%	14.2%
Terminal rate	4/10 (40%)	0/6 (0%)	3/4 (75%)	0/1 (0%)
First incidence (days)	588	584	512	506
Life table test	P=0.436N	P=0.231N	P=0.496N	P=0.431N
Logistic regression test	P=0.069N	P=0.142N	P=0.236N	P=0.065N
Cochran-Armitage test	P=0.023N			
Fisher exact test		P=0.154N	P=0.096N	P=0.027N
Kidney (Renal Tubule): Adenoma (Single Section)				
Overall rate	1/50 (2%)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted rate	10.0%	40.0%	34.9%	24.3%
Terminal rate	1/10 (10%)	2/6 (33%)	0/4 (0%)	0/1 (0%)
First incidence (days)	729 (T)	708	605	566
Life table test	P=0.018	P=0.160	P=0.061	P=0.091
Logistic regression test	P=0.103	P=0.188	P=0.098	P=0.240
Cochran-Armitage test	P=0.282			
Fisher exact test		P=0.309	P=0.181	P=0.309
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	8/50 (16%)	11/50 (22%)	19/50 (38%)	13/50 (26%)
Adjusted rate	44.2%	89.9%	86.9%	71.1%
Terminal rate	3/10 (30%)	5/6 (83%)	2/4 (50%)	0/1 (0%)
First incidence (days)	572	651	525	566
Life table test	P<0.001	P=0.142	P<0.001	P=0.006
Logistic regression test	P=0.011	P=0.278	P=0.002	P=0.074
Cochran-Armitage test	P=0.119			
Fisher exact test		P=0.306	P=0.012	P=0.163

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Section)				
Overall rate	1/50 (2%)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted rate	10.0%	40.0%	34.9%	24.3%
Terminal rate	1/10 (10%)	2/6 (33%)	0/4 (0%)	0/1 (0%)
First incidence (days)	729 (T)	708	605	566
Life table test	P=0.018	P=0.160	P=0.061	P=0.091
Logistic regression test	P=0.103	P=0.188	P=0.098	P=0.240
Cochran-Armitage test	P=0.282			
Fisher exact test		P=0.309	P=0.181	P=0.309
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	8/50 (16%)	13/50 (26%)	19/50 (38%)	13/50 (26%)
Adjusted rate	44.2%	90.7%	86.9%	71.1%
Terminal rate	3/10 (30%)	5/6 (83%)	2/4 (50%)	0/1 (0%)
First incidence (days)	572	624	525	566
Life table test	P<0.001	P=0.073	P<0.001	P=0.006
Logistic regression test	P=0.018	P=0.141	P=0.002	P=0.074
Cochran-Armitage test	P=0.158			
Fisher exact test		P=0.163	P=0.012	P=0.163
Pancreas: Adenoma				
Overall rate	3/50 (6%)	6/49 (12%)	1/50 (2%)	1/50 (2%)
Adjusted rate	22.9%	63.3%	16.7%	2.6%
Terminal rate	1/10 (10%)	3/6 (50%)	0/4 (0%)	0/1 (0%)
First incidence (days)	694	693	685	575
Life table test	P=0.456	P=0.111	P=0.667N	P=0.683
Logistic regression test	P=0.431N	P=0.156	P=0.571N	P=0.513N
Cochran-Armitage test	P=0.094N			
Fisher exact test		P=0.233	P=0.309N	P=0.309N
Pancreas: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	7/49 (14%)	2/50 (4%)	1/50 (2%)
Adjusted rate	22.9%	64.8%	18.9%	2.6%
Terminal rate	1/10 (10%)	3/6 (50%)	0/4 (0%)	0/1 (0%)
First incidence (days)	694	639	551	575
Life table test	P=0.488	P=0.073	P=0.527	P=0.683
Logistic regression test	P=0.321N	P=0.108	P=0.642N	P=0.513N
Cochran-Armitage test	P=0.094N			
Fisher exact test		P=0.151	P=0.500N	P=0.309N
Pancreatic Islets: Adenoma				
Overall rate	15/50 (30%)	15/49 (31%)	7/49 (14%)	6/49 (12%)
Adjusted rate	68.0%	66.3%	51.4%	29.0%
Terminal rate	4/10 (40%)	1/6 (17%)	1/4 (25%)	0/1 (0%)
First incidence (days)	604	520	556	555
Life table test	P=0.438N	P=0.477	P=0.392N	P=0.568N
Logistic regression test	P=0.039N	P=0.575N	P=0.133N	P=0.113N
Cochran-Armitage test	P=0.008N			
Fisher exact test		P=0.560	P=0.050N	P=0.027N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	17/50 (34%)	15/49 (31%)	9/49 (18%)	6/49 (12%)
Adjusted rate	74.5%	66.3%	54.5%	29.0%
Terminal rate	5/10 (50%)	1/6 (17%)	1/4 (25%)	0/1 (0%)
First incidence (days)	604	520	542	555
Life table test	P=0.368N	P=0.538N	P=0.450N	P=0.466N
Logistic regression test	P=0.020N	P=0.389N	P=0.151N	P=0.056N
Cochran-Armitage test	P=0.004N			
Fisher exact test		P=0.442N	P=0.061N	P=0.009N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	33/49 (67%)	33/50 (66%)	31/49 (63%)	23/49 (47%)
Adjusted rate	92.4%	95.9%	100.0%	93.0%
Terminal rate	7/9 (78%)	5/6 (83%)	4/4 (100%)	0/1 (0%)
First incidence (days)	505	395	398	506
Life table test	P=0.113	P=0.467	P=0.115	P=0.253
Logistic regression test	P=0.031N	P=0.491N	P=0.520N	P=0.053N
Cochran-Armitage test	P=0.017N			
Fisher exact test		P=0.528N	P=0.416N	P=0.033N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	33/49 (67%)	33/50 (66%)	31/49 (63%)	23/49 (47%)
Adjusted rate	92.4%	95.9%	100.0%	93.0%
Terminal rate	7/9 (78%)	5/6 (83%)	4/4 (100%)	0/1 (0%)
First incidence (days)	505	395	398	506
Life table test	P=0.113	P=0.467	P=0.115	P=0.253
Logistic regression test	P=0.031N	P=0.491N	P=0.520N	P=0.053N
Cochran-Armitage test	P=0.017N			
Fisher exact test		P=0.528N	P=0.416N	P=0.033N
Preputial Gland: Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	3/50 (6%)	1/49 (2%)
Adjusted rate	2.2%	7.3%	13.0%	2.0%
Terminal rate	0/10 (0%)	0/6 (0%)	0/4 (0%)	0/1 (0%)
First incidence (days)	553	348	589	262
Life table test	P=0.576N	P=0.331	P=0.264	P=0.758N
Logistic regression test	P=0.504N	P=0.247	P=0.306	P=0.721
Cochran-Armitage test	P=0.509N			
Fisher exact test		P=0.309	P=0.309	P=0.747
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	4/50 (8%)	3/49 (6%)
Adjusted rate	15.8%	7.3%	15.7%	100.0%
Terminal rate	1/10 (10%)	0/6 (0%)	0/4 (0%)	1/1 (100%)
First incidence (days)	553	348	582	262
Life table test	P=0.338	P=0.647	P=0.379	P=0.355
Logistic regression test	P=0.572	P=0.640	P=0.477	P=0.661N
Cochran-Armitage test	P=0.547			
Fisher exact test		P=0.661N	P=0.500	P=0.651

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
Skin: Squamous Cell Papilloma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	14.1%	15.4%	12.5%	2.6%
Terminal rate	0/10 (0%)	0/6 (0%)	0/4 (0%)	0/1 (0%)
First incidence (days)	588	591	678	575
Life table test	P=0.394N	P=0.648	P=0.497N	P=0.524N
Logistic regression test	P=0.199N	P=0.660N	P=0.364N	P=0.324N
Cochran-Armitage test	P=0.165N			
Fisher exact test		P=0.661N	P=0.309N	P=0.309N
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rate	14.1%	15.4%	12.5%	16.5%
Terminal rate	0/10 (0%)	0/6 (0%)	0/4 (0%)	0/1 (0%)
First incidence (days)	588	591	678	575
Life table test	P=0.527	P=0.648	P=0.497N	P=0.593
Logistic regression test	P=0.417N	P=0.660N	P=0.364N	P=0.556N
Cochran-Armitage test	P=0.343N			
Fisher exact test		P=0.661N	P=0.309N	P=0.500N
Skin: Keratoacanthoma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	5/50 (10%)	3/50 (6%)
Adjusted rate	14.1%	32.0%	42.4%	18.4%
Terminal rate	0/10 (0%)	1/6 (17%)	1/4 (25%)	0/1 (0%)
First incidence (days)	588	591	556	555
Life table test	P=0.229	P=0.328	P=0.172	P=0.414
Logistic regression test	P=0.544	P=0.361	P=0.283	P=0.645
Cochran-Armitage test	P=0.500N			
Fisher exact test		P=0.357	P=0.357	P=0.661N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	6.7%	17.3%	2.2%	20.0%
Terminal rate	0/10 (0%)	0/6 (0%)	0/4 (0%)	0/1 (0%)
First incidence (days)	692	584	484	679
Life table test	P=0.477	P=0.277	P=0.641	P=0.403
Logistic regression test	P=0.472N	P=0.308	P=0.758N	P=0.602
Cochran-Armitage test	P=0.444N			
Fisher exact test		P=0.309	P=0.753N	P=0.753N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	3/50 (6%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate	15.3%	19.2%	6.2%	22.0%
Terminal rate	0/10 (0%)	0/6 (0%)	0/4 (0%)	0/1 (0%)
First incidence (days)	553	562	484	566
Life table test	P=0.546	P=0.466	P=0.662	P=0.502
Logistic regression test	P=0.325N	P=0.503	P=0.502N	P=0.564N
Cochran-Armitage test	P=0.319N			
Fisher exact test		P=0.500	P=0.500N	P=0.500N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
Testes: Adenoma				
Overall rate	34/50 (68%)	31/50 (62%)	31/50 (62%)	33/50 (66%)
Adjusted rate	96.4%	100.0%	96.2%	100.0%
Terminal rate	9/10 (90%)	6/6 (100%)	3/4 (75%)	1/1 (100%)
First incidence (days)	505	512	484	508
Life table test	P=0.001	P=0.548N	P=0.118	P=0.010
Logistic regression test	P=0.336	P=0.302N	P=0.551N	P=0.516
Cochran-Armitage test	P=0.510N			
Fisher exact test		P=0.338N	P=0.338N	P=0.500N
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/50 (8%)	4/49 (8%)	1/50 (2%)	4/50 (8%)
Adjusted rate	33.0%	36.9%	4.8%	21.3%
Terminal rate	3/10 (30%)	2/6 (33%)	0/4 (0%)	0/1 (0%)
First incidence (days)	636	575	637	594
Life table test	P=0.176	P=0.483	P=0.374N	P=0.171
Logistic regression test	P=0.433	P=0.642	P=0.338N	P=0.412
Cochran-Armitage test	P=0.516N			
Fisher exact test		P=0.631	P=0.181N	P=0.643N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	6/49 (12%)	1/50 (2%)	5/50 (10%)
Adjusted rate	35.2%	41.5%	4.8%	23.0%
Terminal rate	3/10 (30%)	2/6 (33%)	0/4 (0%)	0/1 (0%)
First incidence (days)	603	575	637	555
Life table test	P=0.236	P=0.376	P=0.242N	P=0.193
Logistic regression test	P=0.551	P=0.503	P=0.188N	P=0.493
Cochran-Armitage test	P=0.445N			
Fisher exact test		P=0.486	P=0.102N	P=0.630N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	0/49 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	13.7%	0.0%	0.0%	0.0%
Terminal rate	0/10 (0%)	0/6 (0%)	0/4 (0%)	0/1 (0%)
First incidence (days)	573	–	–	–
Life table test	P=0.028N	P=0.053N	P=0.078N	P=0.104N
Logistic regression test	P=0.019N	P=0.067N	P=0.062N	P=0.062N
Cochran-Armitage test	P=0.020N			
Fisher exact test		P=0.061N	P=0.059N	P=0.059N
All Organs: Mononuclear Cell Leukemia				
Overall rate	30/50 (60%)	28/50 (56%)	24/50 (48%)	23/50 (46%)
Adjusted rate	85.1%	85.1%	100.0%	77.6%
Terminal rate	6/10 (60%)	3/6 (50%)	4/4 (100%)	0/1 (0%)
First incidence (days)	288	553	510	506
Life table test	P=0.085	P=0.523N	P=0.299	P=0.201
Logistic regression test	P=0.142N	P=0.400N	P=0.230N	P=0.137N
Cochran-Armitage test	P=0.079N			
Fisher exact test		P=0.420N	P=0.158N	P=0.115N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	47/50 (94%)	50/50 (100%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	10/10 (100%)	6/6 (100%)	4/4 (100%)	1/1 (100%)
First incidence (days)	505	395	343	262
Life table test	P<0.001	P=0.418	P=0.020	P=0.003
Logistic regression test	P=0.265	P=0.739	P=0.129	P=0.517
Cochran-Armitage test	P=0.313			
Fisher exact test		P=0.661N	P=0.121	P=0.500
All Organs: Malignant Neoplasms				
Overall rate	38/50 (76%)	33/50 (66%)	32/50 (64%)	30/50 (60%)
Adjusted rate	94.0%	87.2%	100.0%	84.6%
Terminal rate	8/10 (80%)	3/6 (50%)	4/4 (100%)	0/1 (0%)
First incidence (days)	288	348	355	262
Life table test	P=0.063	P=0.377N	P=0.245	P=0.152
Logistic regression test	P=0.079N	P=0.176N	P=0.166N	P=0.068N
Cochran-Armitage test	P=0.068N			
Fisher exact test		P=0.189N	P=0.138N	P=0.066N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	50/50 (100%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	10/10 (100%)	6/6 (100%)	4/4 (100%)	1/1 (100%)
First incidence (days)	288	348	343	262
Life table test	P<0.001	P=0.425	P=0.035	P=0.003
Logistic regression test	P=0.372	P=0.504N	P=0.500	P=0.500
Cochran-Armitage test	P=0.236			
Fisher exact test		P=0.753N	P=0.500	P=0.500

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for kidney, pancreas, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE A4
Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Chlorinated and Chloraminated Water	0/51	0/51	0/51
t-Butyl Alcohol	1/50	0/50	1/50
Overall Historical Incidence			
Total	1/277 (0.4%)	0/277 (0.0%)	1/277 (0.4%)
Standard deviation	0.9%		0.9%
Range	0%-2%		0%-2%

[a] Data as of 31 March 1993

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	31	35	41	46
Natural deaths	9	9	5	3
Survivors				
Terminal sacrifice	10	6	4	1
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan				1 (10%)
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan	4 (40%)	2 (20%)	4 (40%)	3 (30%)
Intestine large, cecum	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)			
Intestine small, duodenum	(10)	(10)	(9)	(10)
Ectopic tissue			1 (11%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus	1 (10%)	3 (30%)	2 (20%)	1 (10%)
Clear cell focus		1 (10%)	1 (10%)	1 (10%)
Degeneration, cystic	1 (10%)			
Granuloma	1 (10%)		1 (10%)	
Hepatodiaphragmatic nodule	1 (10%)		1 (10%)	
Hyperplasia, focal			1 (10%)	1 (10%)
Hyperplasia, lymphoid	1 (10%)			
Inflammation, subacute			1 (10%)	
Mixed cell focus				2 (20%)
Bile duct, cyst				1 (10%)
Bile duct, hyperplasia	6 (60%)	8 (80%)	10 (100%)	9 (90%)
Hepatocyte, vacuolization cytoplasmic	1 (10%)	1 (10%)	1 (10%)	
Kupffer cell, pigmentation			1 (10%)	
Mesentery		(1)		
Fat, necrosis		1 (100%)		
Pancreas	(10)	(10)	(10)	(10)
Atrophy	6 (60%)	9 (90%)	5 (50%)	7 (70%)
Hyperplasia, lymphoid	1 (10%)			
Acinar cell, hyperplasia, focal			1 (10%)	
Salivary glands	(10)	(10)	(10)	(10)
Atrophy	1 (10%)			1 (10%)
Stomach, glandular	(10)	(10)	(10)	(10)
Cyst epithelial inclusion		1 (10%)		
Erosion	1 (10%)			
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy	2 (20%)	5 (50%)	4 (40%)	5 (50%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
15-Month Interim Evaluation (continued)				
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	2 (20%)	4 (40%)	5 (50%)	2 (20%)
Hyperplasia, focal	1 (10%)	1 (10%)	1 (10%)	
Vacuolization cytoplasmic, focal	1 (10%)		1 (10%)	2 (20%)
Islets, pancreatic	(10)	(10)	(10)	(10)
Hyperplasia	3 (30%)	1 (10%)	1 (10%)	
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, angiectasis			1 (10%)	1 (11%)
Pars distalis, cyst	1 (10%)			
Pars distalis, hyperplasia			1 (10%)	4 (44%)
Pars nervosa, hyperplasia			1 (10%)	
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, hyperplasia			1 (10%)	
Follicle, cyst	1 (10%)		1 (10%)	1 (10%)
Follicular cell, hyperplasia	1 (10%)			
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Atypia cellular		2 (20%)	1 (10%)	3 (30%)
Preputial gland	(10)	(10)	(10)	(10)
Inflammation, chronic	2 (20%)	6 (60%)	4 (40%)	5 (50%)
Inflammation, suppurative	3 (30%)	2 (20%)	1 (10%)	1 (10%)
Necrosis		1 (10%)		
Prostate	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid	3 (30%)	1 (10%)	2 (20%)	2 (20%)
Inflammation, suppurative	7 (70%)	6 (60%)	7 (70%)	7 (70%)
Testes	(10)	(10)	(10)	(10)
Interstitial cell, hyperplasia	3 (30%)	6 (60%)	2 (20%)	6 (60%)
Seminiferous tubule, atrophy				1 (10%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Myelofibrosis	1 (10%)			
Lymph node			(1)	(1)
Mediastinal, hemorrhage			1 (100%)	1 (100%)
Lymph node, mandibular	(10)	(10)	(10)	(10)
Ectasia	1 (10%)	1 (10%)		1 (10%)
Hemorrhage	1 (10%)	2 (20%)	2 (20%)	
Hyperplasia, lymphoid			2 (20%)	1 (10%)
Hyperplasia, plasma cell	2 (20%)	1 (10%)	1 (10%)	
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid		2 (20%)	3 (30%)	
Infiltration cellular, mast cell				1 (10%)
Spleen	(10)	(10)	(10)	(10)
Developmental malformation		1 (10%)	1 (10%)	
Fibrosis			1 (10%)	1 (10%)
Pigmentation		1 (10%)	1 (10%)	1 (10%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
15-Month Interim Evaluation (continued)				
Integumentary System				
Mammary gland	(10)	(8)	(10)	(9)
Hyperplasia, cystic	2 (20%)	2 (25%)	1 (10%)	1 (11%)
Skin	(10)	(10)	(10)	(10)
Acanthosis			1 (10%)	
Nervous System				
Brain	(10)	(10)	(10)	(10)
Compression	2 (20%)	1 (10%)	1 (10%)	
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Hemorrhage		1 (10%)		
Infiltration cellular, histiocyte	3 (30%)		2 (20%)	1 (10%)
Inflammation, subacute	1 (10%)	1 (10%)	3 (30%)	1 (10%)
Alveolar epithelium, hyperplasia	1 (10%)			
Nose	(10)	(10)	(10)	(10)
Exudate	4 (40%)	3 (30%)	7 (70%)	4 (40%)
Foreign body	2 (20%)	3 (30%)	2 (20%)	3 (30%)
Fungus		2 (20%)	4 (40%)	1 (10%)
Mucosa, hyperplasia	2 (20%)	3 (30%)	3 (30%)	1 (10%)
Mucosa, metaplasia, squamous		2 (20%)	4 (40%)	
Special Senses System				
Eye		(1)		(1)
Cataract		1 (100%)		1 (100%)
Retina, atrophy		1 (100%)		1 (100%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization	1 (10%)	2 (20%)	5 (50%)	9 (90%)
Nephropathy	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Urinary bladder	(10)	(10)	(10)	(10)
Angiectasis			1 (10%)	
Systems Examined With No Lesions Observed				
General Body System				
Musculoskeletal System				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(49)	(50)	(50)
Parasite metazoan	5 (10%)	4 (8%)	4 (8%)	4 (8%)
Intestine large, rectum	(49)	(48)	(49)	(50)
Parasite metazoan	2 (4%)	5 (10%)	2 (4%)	3 (6%)
Intestine large, cecum	(50)	(49)	(50)	(50)
Dilatation	1 (2%)	1 (2%)		1 (2%)
Edema	1 (2%)			1 (2%)
Erosion	1 (2%)			
Hyperplasia, lymphoid			1 (2%)	
Parasite metazoan	1 (2%)			1 (2%)
Intestine small, duodenum	(48)	(43)	(46)	(50)
Erosion	2 (4%)	3 (7%)	8 (17%)	4 (8%)
Inflammation, suppurative			1 (2%)	
Ulcer		1 (2%)		
Mucosa, hyperplasia, diffuse		1 (2%)		2 (4%)
Intestine small, jejunum	(50)	(47)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)			
Inflammation, subacute		1 (2%)		
Mucosa, hyperplasia, diffuse	3 (6%)	3 (6%)	4 (8%)	1 (2%)
Intestine small, ileum	(50)	(48)	(49)	(50)
Dilatation	1 (2%)			1 (2%)
Fibrosis	1 (2%)			
Inflammation, chronic	1 (2%)			
Inflammation, subacute		1 (2%)		
Metaplasia, osseous	1 (2%)			
Mucosa, hyperplasia, diffuse		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Angiectasis	3 (6%)	2 (4%)	6 (12%)	4 (8%)
Basophilic focus	12 (24%)	16 (32%)	22 (44%)	17 (34%)
Clear cell focus	6 (12%)	3 (6%)	2 (4%)	4 (8%)
Congestion	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Degeneration, cystic	10 (20%)	8 (16%)	8 (16%)	6 (12%)
Eosinophilic focus	2 (4%)	3 (6%)		3 (6%)
Granuloma	2 (4%)	3 (6%)	5 (10%)	2 (4%)
Hematopoietic cell proliferation	3 (6%)	3 (6%)		2 (4%)
Hemorrhage			1 (2%)	
Hepatodiaphragmatic nodule	9 (18%)	8 (16%)	5 (10%)	3 (6%)
Hyperplasia, focal	9 (18%)	7 (14%)	3 (6%)	5 (10%)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, subacute	1 (2%)	3 (6%)	3 (6%)	4 (8%)
Mixed cell focus	6 (12%)	3 (6%)	3 (6%)	1 (2%)
Thrombosis		1 (2%)		
Bile duct, cyst	1 (2%)		1 (2%)	
Bile duct, hyperplasia	42 (84%)	41 (82%)	37 (74%)	46 (92%)
Centrilobular, atrophy	9 (18%)	12 (24%)	7 (14%)	16 (32%)
Centrilobular, necrosis		1 (2%)	2 (4%)	2 (4%)
Hepatocyte, vacuolization cytoplasmic	15 (30%)	13 (26%)	12 (24%)	4 (8%)
Kupffer cell, pigmentation	3 (6%)	8 (16%)	3 (6%)	2 (4%)
Lobules, necrosis	4 (8%)	7 (14%)	3 (6%)	1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(5)	(6)	(9)	(3)
Accessory spleen			1 (11%)	1 (33%)
Hemorrhage		1 (17%)		
Fat, hemorrhage	1 (20%)			
Fat, necrosis	5 (100%)	4 (67%)	4 (44%)	1 (33%)
Pancreas	(50)	(49)	(50)	(50)
Atrophy	28 (56%)	28 (57%)	28 (56%)	18 (36%)
Cyst	1 (2%)			3 (6%)
Fibrosis	1 (2%)			
Focal cellular change	1 (2%)		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	1 (2%)	
Acinar cell, cytoplasmic alteration	8 (16%)	11 (22%)	13 (26%)	11 (22%)
Acinar cell, hyperplasia, focal	10 (20%)	5 (10%)	6 (12%)	1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Acinar cell, cytoplasmic alteration	5 (10%)	5 (10%)	4 (8%)	4 (8%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	4 (8%)	7 (14%)	4 (8%)	2 (4%)
Erosion	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Fibrosis		3 (6%)	1 (2%)	
Hyperplasia	1 (2%)			
Inflammation, subacute	2 (4%)	1 (2%)		1 (2%)
Perforation		1 (2%)		
Ulcer	7 (14%)	14 (28%)	9 (18%)	3 (6%)
Mucosa, hyperplasia	12 (24%)	16 (32%)	10 (20%)	7 (14%)
Stomach, glandular	(50)	(49)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Edema	6 (12%)	2 (4%)	5 (10%)	3 (6%)
Erosion	10 (20%)	5 (10%)	6 (12%)	6 (12%)
Inflammation, chronic	1 (2%)	3 (6%)		
Mineralization	4 (8%)	3 (6%)	2 (4%)	2 (4%)
Ulcer	2 (4%)	3 (6%)	7 (14%)	2 (4%)
Epithelium, dilatation		2 (4%)		
Cardiovascular System				
Blood vessel	(6)	(3)	(1)	(1)
Hypertrophy	2 (33%)			1 (100%)
Inflammation, chronic active	6 (100%)	3 (100%)	1 (100%)	1 (100%)
Thrombosis				1 (100%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	24 (48%)	25 (50%)	25 (50%)	23 (46%)
Thrombosis	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Myocardium, inflammation, chronic				1 (2%)
Myocardium, mineralization	1 (2%)		1 (2%)	1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	12 (24%)	13 (26%)	10 (20%)	12 (24%)
Atrophy	1 (2%)			
Basophilic focus		2 (4%)		1 (2%)
Congestion	1 (2%)	1 (2%)		
Cyst	1 (2%)			
Hematopoietic cell proliferation	1 (2%)	2 (4%)		
Hemorrhage	1 (2%)			
Hyperplasia, diffuse	1 (2%)			
Hyperplasia, focal	5 (10%)	4 (8%)	6 (12%)	4 (8%)
Hypertrophy, focal	4 (8%)	1 (2%)	2 (4%)	
Necrosis				1 (2%)
Pigmentation	3 (6%)	3 (6%)	1 (2%)	2 (4%)
Vacuolization cytoplasmic, diffuse	6 (12%)	6 (12%)	4 (8%)	1 (2%)
Vacuolization cytoplasmic, focal	15 (30%)	9 (18%)	16 (32%)	13 (26%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	22 (44%)	21 (42%)	23 (46%)	15 (30%)
Islets, pancreatic	(50)	(49)	(49)	(49)
Hyperplasia	2 (4%)	1 (2%)	2 (4%)	4 (8%)
Parathyroid gland	(50)	(46)	(49)	(48)
Hyperplasia	8 (16%)	9 (20%)	13 (27%)	6 (13%)
Pituitary gland	(49)	(50)	(49)	(49)
Inflammation, suppurative		1 (2%)		
Pigmentation				2 (4%)
Pars distalis, angiectasis	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Pars distalis, cyst	3 (6%)	4 (8%)	2 (4%)	
Pars distalis, hyperplasia	9 (18%)	7 (14%)	8 (16%)	9 (18%)
Pars distalis, necrosis		1 (2%)		
Pars intermedia, angiectasis	1 (2%)	1 (2%)		
Pars intermedia, cyst	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Pars nervosa, hyperplasia	4 (8%)	4 (8%)	3 (6%)	11 (22%)
Thyroid gland	(50)	(49)	(50)	(50)
Degeneration, cystic	4 (8%)	1 (2%)		3 (6%)
Hypoplasia				1 (2%)
Infiltration cellular, histiocyte	1 (2%)		1 (2%)	
Ultimobranchial cyst		2 (4%)	1 (2%)	2 (4%)
C-cell, hyperplasia	11 (22%)	9 (18%)	1 (2%)	3 (6%)
Follicle, cyst	6 (12%)	2 (4%)	5 (10%)	6 (12%)
Follicular cell, hyperplasia	3 (6%)			
General Body System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
2-Year Study (continued)				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Atypia cellular	15 (30%)	7 (14%)	10 (20%)	7 (14%)
Hypospermia	26 (52%)	22 (44%)	19 (38%)	23 (46%)
Penis		(2)	(1)	
Edema		1 (50%)		
Inflammation, suppurative		2 (100%)	1 (100%)	
Preputial gland	(50)	(50)	(50)	(49)
Ectasia	2 (4%)	3 (6%)	1 (2%)	
Hyperplasia	1 (2%)			
Inflammation, chronic	21 (42%)	20 (40%)	19 (38%)	22 (45%)
Inflammation, suppurative	4 (8%)	3 (6%)	4 (8%)	5 (10%)
Prostate	(50)	(50)	(50)	(50)
Corpora amylacea	7 (14%)	7 (14%)	9 (18%)	7 (14%)
Ectasia	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Fibrosis	3 (6%)	4 (8%)	3 (6%)	3 (6%)
Hyperplasia, lymphoid	8 (16%)	7 (14%)	7 (14%)	6 (12%)
Inflammation, suppurative	45 (90%)	42 (84%)	39 (78%)	30 (60%)
Epithelium, hyperplasia	2 (4%)		2 (4%)	2 (4%)
Seminal vesicle	(50)	(50)	(50)	(50)
Depletion cellular				1 (2%)
Fibrosis			1 (2%)	
Inflammation, chronic		1 (2%)		
Inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Testes	(50)	(50)	(50)	(50)
Mineralization	2 (4%)		1 (2%)	
Spermatocele	1 (2%)			
Interstitial cell, hyperplasia	8 (16%)	14 (28%)	9 (18%)	14 (28%)
Seminiferous tubule, atrophy	14 (28%)	18 (36%)	10 (20%)	12 (24%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Hypercellularity		1 (2%)	4 (8%)	2 (4%)
Myelofibrosis	3 (6%)	4 (8%)	2 (4%)	4 (8%)
Lymph node	(19)	(11)	(14)	(19)
Inguinal, hyperplasia, plasma cell				1 (5%)
Lumbar, hyperplasia, plasma cell		1 (9%)		
Mediastinal, hemorrhage	3 (16%)	1 (9%)	2 (14%)	1 (5%)
Mediastinal, hyperplasia, lymphoid				1 (5%)
Mediastinal, hyperplasia, plasma cell	1 (5%)		1 (7%)	
Mediastinal, necrosis			1 (7%)	
Mediastinal, pigmentation	1 (5%)			
Pancreatic, ectasia	1 (5%)			
Pancreatic, hemorrhage				1 (5%)
Pancreatic, hyperplasia, lymphoid				1 (5%)
Pancreatic, pigmentation		1 (9%)		
Renal, hemorrhage	1 (5%)	1 (9%)		
Renal, hyperplasia, plasma cell		1 (9%)		
Renal, pigmentation	1 (5%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(50)	(48)	(49)	(50)
Congestion			1 (2%)	
Ectasia	4 (8%)	8 (17%)	4 (8%)	6 (12%)
Fibrosis		1 (2%)		1 (2%)
Hemorrhage	3 (6%)	4 (8%)		
Hyperplasia, lymphoid	1 (2%)	3 (6%)	6 (12%)	2 (4%)
Hyperplasia, plasma cell	13 (26%)	18 (38%)	10 (20%)	11 (22%)
Inflammation, suppurative	1 (2%)			
Lymph node, mesenteric	(49)	(49)	(50)	(50)
Ectasia	1 (2%)	1 (2%)	2 (4%)	
Hemorrhage	3 (6%)	4 (8%)	1 (2%)	5 (10%)
Hyperplasia, lymphoid	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Pigmentation		2 (4%)		
Spleen	(50)	(49)	(50)	(50)
Congestion		1 (2%)		
Developmental malformation	2 (4%)			
Fibrosis	11 (22%)	17 (35%)	13 (26%)	13 (26%)
Hematopoietic cell proliferation	9 (18%)	12 (24%)	12 (24%)	12 (24%)
Infiltration cellular, histiocyte	1 (2%)			
Necrosis	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Pigmentation	21 (42%)	34 (69%)	22 (44%)	24 (48%)
Lymphoid follicle, atrophy	2 (4%)	2 (4%)		
Red pulp, atrophy	2 (4%)	1 (2%)		
Thymus	(45)	(49)	(48)	(47)
Congestion	1 (2%)			
Cyst				3 (6%)
Ectopic parathyroid gland				1 (2%)
Ectopic thyroid		1 (2%)		
Hemorrhage	1 (2%)			
Epithelial cell, hyperplasia				1 (2%)
Integumentary System				
Mammary gland	(44)	(50)	(47)	(47)
Hyperplasia, cystic	24 (55%)	28 (56%)	26 (55%)	15 (32%)
Hyperplasia, lobular	2 (5%)	2 (4%)		
Skin	(50)	(50)	(49)	(50)
Acanthosis	4 (8%)	3 (6%)	1 (2%)	2 (4%)
Cyst epithelial inclusion	1 (2%)	1 (2%)	1 (2%)	
Exudate	2 (4%)	1 (2%)	1 (2%)	
Hyperplasia, basal cell		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	10 (20%)	14 (28%)	16 (32%)	10 (20%)
Hyperostosis		2 (4%)		1 (2%)
Necrosis		1 (2%)		1 (2%)
Femur, osteopetrosis	1 (2%)			1 (2%)
Sternum, osteopetrosis	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
2-Year Study (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	17 (34%)	17 (34%)	18 (36%)	6 (12%)
Granuloma			1 (2%)	
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hydrocephalus	6 (12%)	10 (20%)	12 (24%)	5 (10%)
Mineralization		1 (2%)		2 (4%)
Necrosis				3 (6%)
Vacuolization cytoplasmic	1 (2%)		1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	4 (8%)	1 (2%)	4 (8%)	
Edema		1 (2%)		
Foreign body		1 (2%)		1 (2%)
Hemorrhage		1 (2%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid		3 (6%)	2 (4%)	
Infiltration cellular, histiocyte	12 (24%)	12 (24%)	10 (20%)	14 (28%)
Inflammation, subacute	1 (2%)	4 (8%)	4 (8%)	1 (2%)
Inflammation, suppurative		2 (4%)		1 (2%)
Leukocytosis			1 (2%)	
Metaplasia, osseous	2 (4%)		1 (2%)	
Alveolar epithelium, hyperplasia	5 (10%)	2 (4%)	6 (12%)	5 (10%)
Nose	(50)	(50)	(50)	(50)
Exudate	26 (52%)	23 (46%)	27 (54%)	20 (40%)
Foreign body	14 (28%)	14 (28%)	16 (32%)	9 (18%)
Fungus	17 (34%)	15 (30%)	18 (36%)	13 (26%)
Mucosa, hyperplasia	23 (46%)	21 (42%)	21 (42%)	20 (40%)
Mucosa, metaplasia, squamous	6 (12%)	7 (14%)	5 (10%)	7 (14%)
Mucosa, necrosis		2 (4%)		4 (8%)
Trachea	(50)	(50)	(50)	(50)
Mucosa, hyperplasia		1 (2%)		
Special Senses System				
Eye	(4)	(2)	(2)	(2)
Cataract	4 (100%)	2 (100%)	1 (50%)	2 (100%)
Inflammation, chronic		1 (50%)		
Retina, atrophy	4 (100%)	2 (100%)		2 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst				1 (2%)
Hemorrhage				1 (2%)
Hydronephrosis		1 (2%)		1 (2%)
Hyperplasia, lymphoid				1 (2%)
Inflammation, suppurative	10 (20%)	18 (36%)	12 (24%)	9 (18%)
Mineralization	26 (52%)	28 (56%)	35 (70%)	48 (96%)
Nephropathy	49 (98%)	49 (98%)	50 (100%)	50 (100%)
Thrombosis				1 (2%)
Interstitial tissue, pigmentation				1 (2%)
Renal tubule, cytoplasmic alteration			1 (2%)	
Renal tubule, hyperplasia	3 (6%)	7 (14%)	6 (12%)	6 (12%)
Renal tubule, hyperplasia, oncocytic			2 (4%)	
Renal tubule, pigmentation	7 (14%)	9 (18%)	6 (12%)	12 (24%)
Transitional epithelium, hyperplasia	25 (50%)	32 (64%)	36 (72%)	40 (80%)
Urinary bladder	(50)	(50)	(50)	(50)
Dilatation	2 (4%)		2 (4%)	2 (4%)
Hemorrhage	1 (2%)	1 (2%)		1 (2%)
Inflammation, subacute			1 (2%)	
Inflammation, suppurative	1 (2%)	2 (4%)		
Mucosa, hyperplasia			3 (6%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *t*-BUTYL ALCOHOL

TABLE B1 Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 113

TABLE B2 Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 118

TABLE B3 Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 138

TABLE B4 Historical Incidence of Renal Tubule Neoplasms in Untreated Female F344/N Rats 144

TABLE B5 Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 145

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	15	18	21	35
Natural deaths	7	8	7	3
Survivors				
Terminal sacrifice	28	24	22	12
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Adrenal medulla	(10)	(10)	(10)	(10)
Pheochromocytoma malignant				1 (10%)
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, adenoma	3 (30%)	3 (30%)	2 (20%)	3 (30%)
Pars distalis, carcinoma	1 (10%)			
Thyroid gland	(9)	(10)	(10)	(10)
C-cell, adenoma	1 (11%)			
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Adenoma		1 (10%)		
Uterus	(10)	(10)	(10)	(10)
Adenoma	1 (10%)			
Polyp stromal	3 (30%)	1 (10%)	2 (20%)	1 (10%)
Hematopoietic System				
Spleen	(10)	(10)	(10)	(10)
Thymus	(10)	(10)	(10)	(10)
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Fibroadenoma	2 (20%)	1 (10%)		
Musculoskeletal System				
Bone	(10)	(10)	(10)	(10)
Osteosarcoma			1 (10%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar carcinoma			1 (10%)	
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia mononuclear			1 (10%)	1 (10%)
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine small, duodenum	(50)	(50)	(49)	(50)
Intestine small, jejunum	(50)	(49)	(49)	(50)
Adenoma				1 (2%)
Liver	(50)	(50)	(50)	(50)
Fibrosarcoma	1 (2%)			
Fibrosarcoma, metastatic, skin		1 (2%)		
Hepatocellular adenoma	1 (2%)	1 (2%)		1 (2%)
Mesentery	(8)	(6)	(8)	(6)
Carcinoma, metastatic, uterus			1 (13%)	
Sarcoma stromal, metastatic, uterus			1 (13%)	
Pancreas	(50)	(50)	(49)	(50)
Carcinoma, metastatic, uterus			1 (2%)	
Pharynx				(1)
Squamous cell papilloma				1 (100%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Carcinoid tumor benign			1 (2%)	
Tongue		(1)	(1)	(3)
Squamous cell carcinoma			1 (100%)	
Squamous cell papilloma		1 (100%)		1 (33%)
Tooth, gingiva		(2)		
Squamous cell carcinoma		1 (50%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)		1 (2%)
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma malignant		1 (2%)		
Pheochromocytoma complex			1 (2%)	
Pheochromocytoma benign	3 (6%)		1 (2%)	2 (4%)
Islets, pancreatic	(50)	(50)	(48)	(50)
Adenoma	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Carcinoma	1 (2%)			
Pituitary gland	(50)	(50)	(49)	(49)
Pars distalis, adenoma	30 (60%)	29 (58%)	26 (53%)	27 (55%)
Pars distalis, carcinoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pars intermedia, adenoma	1 (2%)	1 (2%)	1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	7 (14%)	4 (8%)	6 (12%)	9 (18%)
C-cell, carcinoma	1 (2%)			
Follicular cell, adenoma	1 (2%)		1 (2%)	
Follicular cell, carcinoma	1 (2%)		1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(49)	(50)	(50)	(50)
Adenoma	4 (8%)	5 (10%)	4 (8%)	2 (4%)
Carcinoma	3 (6%)	2 (4%)	6 (12%)	4 (8%)
Ovary	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Granulosa cell tumor benign	1 (2%)			
Granulosa-theca tumor benign	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Carcinoma	1 (2%)		1 (2%)	
Carcinoma in situ		1 (2%)		
Hemangiosarcoma			1 (2%)	
Leiomyoma	1 (2%)	1 (2%)		
Polyp stromal	11 (22%)	5 (10%)	7 (14%)	6 (12%)
Sarcoma stromal			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(14)	(15)	(9)	(7)
Lymph node, mandibular	(50)	(49)	(50)	(49)
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
Lymph node, mesenteric	(50)	(49)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Thymus	(48)	(47)	(49)	(48)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(49)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Carcinoma	6 (12%)	5 (10%)	1 (2%)	1 (2%)
Fibroadenoma	12 (24%)	14 (29%)	11 (22%)	8 (16%)
Skin	(50)	(50)	(49)	(50)
Basal cell adenoma				1 (2%)
Keratoacanthoma			1 (2%)	
Squamous cell carcinoma				1 (2%)
Subcutaneous tissue, fibroma		1 (2%)	1 (2%)	
Subcutaneous tissue, fibrosarcoma	2 (4%)	3 (6%)		
Subcutaneous tissue, lipoma				1 (2%)
Musculoskeletal System				
Skeletal muscle		(1)	(1)	(1)
Squamous cell carcinoma, metastatic, skin				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Oligodendroglioma malignant		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma				2 (4%)
Alveolar/bronchiolar adenoma, multiple, two			1 (2%)	
Alveolar/bronchiolar carcinoma		1 (2%)		
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
Fibrosarcoma, metastatic, skin	1 (2%)	1 (2%)		
Nose	(50)	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)	
Special Senses System				
Zymbal's gland	(2)	(1)		(1)
Carcinoma	2 (100%)	1 (100%)		1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Urinary bladder	(50)	(50)	(50)	(50)
Carcinoma, metastatic, uterus			1 (2%)	
Sarcoma stromal, metastatic, uterus			1 (2%)	
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Leukemia mononuclear	22 (44%)	20 (40%)	18 (36%)	13 (26%)
Mesothelioma malignant	1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
2-Year Study (continued)				
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	6	4	5	5
2-Year study	48	47	43	45
Total primary neoplasms				
15-Month interim evaluation	11	6	7	6
2-Year study	119	102	101	86
Total animals with benign neoplasms				
15-Month interim evaluation	5	4	2	3
2-Year study	43	41	38	36
Total benign neoplasms				
15-Month interim evaluation	10	6	4	4
2-Year study	77	65	68	65
Total animals with malignant neoplasms				
15-Month interim evaluation	1		3	2
2-Year study	32	31	26	20
Total malignant neoplasms				
15-Month interim evaluation	1		3	2
2-Year study	42	37	33	21
Total animals with metastatic neoplasms				
2-Year study	2	1	2	1
Total metastatic neoplasms				
2-Year study	3	4	5	1

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL

Number of Days on Study	226	228	245	247	255	276	280	289	291	294	303	304	225	227	233	245	246	250	274	280	295	223	229	229	229
Carcass ID Number	253	246	247	278	259	288	284	249	256	251	267	287	270	243	254	279	296	284	297	255	264	277	241	242	248
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma	X																								
Hepatocellular adenoma																									
Mesentery																	+		+				+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X																
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X				X		X		X		X		X		X	X			X			X
Pars distalis, carcinoma																					X				
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X												X
C-cell, carcinoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																		X							
General Body System																									
None																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	252	257	260	261	262	265	266	269	271	273	274	275	280	282	283	285	289	290	291	292	293	295	298	299	300	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Hepatocellular adenoma																		X								1
Mesentery			+					+	+			+				+										8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign													X												X	3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma		X																								1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X			X		30
Pars distalis, carcinoma																										1
Pars intermedia, adenoma																									X	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma										X		X			X	X				X						7
C-cell, carcinoma																			X							1
Follicular cell, adenoma										X																1
Follicular cell, carcinoma																										1
General Body System																										
None																										

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	226	228	244	247	254	257	280	289	291	294	303	304	325	327	337	345	346	360	374	380	395	723	729	729	729
Carcass ID Number	253	246	247	278	259	288	244	249	256	251	267	287	270	243	254	279	296	284	297	255	264	277	241	242	248
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X					X			X	
Carcinoma																						X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign											X														
Granulosa-theca tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X																
Leiomyoma															X										
Polyp stromal				X																X			X	X	
Vagina			+												M				M						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+		+	+	+	+	+	+	+							+	+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma													X								X	X			
Fibroadenoma								X				X	X		X	X			X		X	X	X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																									
Fibrosarcoma, metastatic, skin																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									+
Eye				+									+												
Zymbal's gland		+																							
Carcinoma		X																							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	252	257	260	261	262	265	266	269	271	273	274	275	280	282	283	285	289	290	291	292	293	295	298	299	300	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																					X					4
Carcinoma																				X		X				3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																										1
Granulosa-theca tumor benign																									X	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Leiomyoma																										1
Polyp stromal				X							X	X			X			X				X		X		11
Vagina				+			+					M														3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node											+												+			14
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland	X																									1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X						X																			2
Carcinoma																	X			X				X		6
Fibroadenoma			X	X											X											12
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																	X									2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland	X																									1
Fibrosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye																										2
Zymbal's gland	+																									2
Carcinoma	X																									2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	226	228	224	247	254	276	280	289	291	294	303	304	225	227	237	245	246	250	274	280	295	273	229	229	229
Carcass ID Number	253	246	247	278	259	258	244	249	256	251	267	287	270	243	254	279	296	284	297	255	264	277	241	242	248
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X			X	X	X	X	X				X		X		X	X			X		X
Mesothelioma malignant																	X								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	252	257	260	261	262	265	266	269	271	273	274	275	280	282	283	285	289	290	291	292	293	295	298	299	300	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X	X				X	X							X			X	X	X	X	22
Mesothelioma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 2.5 mg/mL

Number of Days on Study	232	324	424	430	502	533	542	552	552	589	590	591	593	610	611	612	618	624	625	645	646	647	703	703	723
Carcass ID Number	326	327	301	357	521	512	446	409	325	515	352	357	350	443	442	448	447	435	439	331	320	314	329	344	328
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin														X											
Hepatocellular adenoma																									
Mesentery		+							+																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Tooth, gingiva											+												+		
Squamous cell carcinoma																							X		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X					X			X	X	X	X			X		X	X		X	
Pars distalis, carcinoma																		X							
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X				X																	
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X				X				
Carcinoma												X													
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin														X											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 2.5 mg/mL
(continued)

Number of Days on Study	727	731	733	734	735	736	738	740	741	743	749	752	754	760	762	763	766	770	771	775	773	775	776	778	779	
Carcass ID Number	313	302	303	304	305	306	308	310	316	318	319	322	324	330	332	333	336	340	341	345	353	355	356	358	359	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Hepatocellular adenoma																					X					1
Mesentery	+		+																		+				+	6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue	+																									1
Squamous cell papilloma	X																									1
Tooth, gingiva																										2
Squamous cell carcinoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant				X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X	X	X	X	X	X	X		X	X	X	X		X				X		X	X	X	29
Pars distalis, carcinoma																										1
Pars intermedia, adenoma		X																								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																						X	X			4
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X							X		X											5
Carcinoma								X																		2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 2.5 mg/mL
(continued)

Number of Days on Study	232	324	424	430	502	533	542	552	552	589	590	591	593	610	611	612	618	624	625	644	646	647	703	703	723
Carcass ID Number	326	327	301	357	321	312	346	309	325	315	352	337	350	343	342	348	347	335	339	331	320	314	329	354	328
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma in situ																	X								
Leiomyoma									X																
Polyp stromal																				X		X			
Vagina							+			+						M						+			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+			+	+	+							+	+			+	+	+			+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin														X											
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adenoma																									
Carcinoma																					X			X	
Fibroadenoma						X				X									X					X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant		X																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, skin														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear														+											
Eye																							+		
Zymbal's gland											+														
Carcinoma											X														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X				X	X			X		X		X	X			X	X	X	X	X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 2.5 mg/mL
(continued)

Number of Days on Study	727	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	313	302	303	304	305	306	308	310	316	318	319	322	324	330	332	333	336	340	341	345	353	355	356	358	359	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma in situ																										1
Leiomyoma																										1
Polyp stromal															X					X			X			5
Vagina									M																	3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+								+					+		+										15
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X																							1
Carcinoma			X											X											X	5
Fibroadenoma	X	X	X													X	X		X	X	X	X			X	14
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma					X																					1
Subcutaneous tissue, fibrosarcoma		X													X											3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																							X			1
Fibrosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye						+									+			+				+				5
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X			X			X				X										20

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL

Number of Days on Study	255	321	332	377	384	459	468	534	626	633	665	733	755	798	637	639	645	651	652	667	694	694	699	701	703
Carcass ID Number	402	406	382	375	390	401	378	383	362	399	367	369	365	400	366	401	411	374	386	408	377	419	363	387	371
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery							+						+												+
Carcinoma, metastatic, uterus																									
Sarcoma stromal, metastatic, uterus							X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor benign																									X
Tongue																		+							
Squamous cell carcinoma																		X							
Cardiovascular System																									
Blood vessel						+																			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex											X														
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X		X					X		X		X					X	X	X	X	X	
Pars distalis, carcinoma																									X
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X				X					X			X
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	703	708	724	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	
Carcass ID Number	407	391	380	361	364	370	373	376	381	385	389	392	393	395	396	398	403	404	409	416	417	418	420	422	413	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+	+									+				+	+							8
Carcinoma, metastatic, uterus														X												1
Sarcoma stromal, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, uterus														X												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor benign																										1
Tongue																										1
Squamous cell carcinoma																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex																										1
Pheochromocytoma benign													X													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma			X					X										X			X					4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X	X	X				X	X		X	X	X		X	X				X		X	X	X	26
Pars distalis, carcinoma																										1
Pars intermedia, adenoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X																		X			6
Follicular cell, adenoma									X																	1
Follicular cell, carcinoma															X											1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	2	3	3	3	3	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	
	5	2	3	7	8	5	6	3	6	6	6	7	7	9	3	3	4	5	5	6	9	9	9	0	0	
	5	1	2	7	4	9	8	4	2	3	5	3	5	8	7	9	5	1	2	7	4	4	9	1	3	
Carcass ID Number	4	4	3	3	3	4	3	3	3	3	3	3	3	4	3	4	4	3	3	4	3	4	3	3	3	
	0	0	8	7	9	0	7	8	6	9	6	6	6	0	6	1	1	7	8	0	7	1	6	8	7	
	2	6	2	5	0	1	8	3	2	9	7	9	5	0	6	0	4	4	6	8	7	9	3	7	1	
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																							X			
Carcinoma																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																										
Carcinoma																										
Hemangiosarcoma																										
Polyp stromal							X					X					X									
Sarcoma stromal							X																			
Vagina									+	+		+		+		+							M			
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node	+											+						+	+				+		+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																					X		X			
Carcinoma																										
Fibroadenoma																			X		X		X		X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	
Keratoacanthoma																		X								
Subcutaneous tissue, fibroma									X																	
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle																	+									
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spinal cord																			+							
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma, multiple, two																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Squamous cell carcinoma				X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	703	708	724	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	
Carcass ID Number	407	391	380	361	364	370	373	376	381	385	389	392	393	395	396	398	403	404	409	416	417	418	420	421	413	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X					X					X							X		4
Carcinoma		X									X								X	X		X				6
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															1
Carcinoma														X												1
Hemangiosarcoma			X																							1
Polyp stromal		X		X									X						X							7
Sarcoma stromal																										1
Vagina		M	M			M								+											M	6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+				+						+													9
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Carcinoma		X																								1
Fibroadenoma										X		X	X					X				X	X		X	11
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma																										1
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma, multiple, two																									X	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	255	321	332	377	384	459	468	534	562	563	565	573	575	598	637	639	645	651	652	667	694	694	699	701	703
Carcass ID Number	402	406	382	375	390	401	378	383	362	399	367	369	365	400	366	410	414	374	386	408	377	419	363	387	371
Special Senses System																									
Eye							+																		
Lacrimal gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus																									
Sarcoma stromal, metastatic, uterus							X																		
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X					X	X	X	X	X	X	X					X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	703	708	724	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	
Carcass ID Number	407	391	380	361	364	370	373	376	381	385	389	392	393	395	396	398	403	404	409	416	417	418	420	421	413	Total Tissues/ Tumors
Special Senses System																										
Eye					+					+	+			+												5
Lacrimal gland																							+			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uterus														X												1
Sarcoma stromal, metastatic, uterus																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X		X						X	X				X	X	X					X	18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL

Number of Days on Study	206	476	511	551	555	576	590	591	591	597	597	597	605	610	610	610	617	617	624	624	625	625	625	631	636
Carcass ID Number	437	435	428	455	450	429	478	431	449	434	469	470	463	424	427	667	470	473	454	468	432	439	471	447	466
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																						X			
Mesentery					+						+														+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx												+													
Squamous cell papilloma												X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue											+											+		+	
Squamous cell papilloma																						X			
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X	X			X		X				X			X		X			X	X
Pars distalis, carcinoma					X																				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma															X				X			X			X
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma																X									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal										X		X			X	X									
Vagina			+												+									+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	643	666	667	674	685	685	693	703	703	703	708	727	730	730	730	730	730	730	730	730	730	730	730	730		
Carcass ID Number	453	451	459	442	444	456	476	475	446	452	480	462	479	422	423	426	438	441	443	445	457	460	461	465	474	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery											+									+				+		6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										3
Squamous cell papilloma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									X	1
Adrenal medulla	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign															X											2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																								1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X		X		X	X		X	X	X		X	X	X	X		X	X	X	X	X		X	27
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X		X	X		X												X	9
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			2
Carcinoma								X				X											X			4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X									X												6
Vagina					M	M				+															+	6

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	206	476	511	551	555	576	590	591	599	597	599	590	605	610	610	610	617	617	624	624	625	625	625	631	636
Carcass ID Number	437	435	428	455	450	429	478	431	449	434	469	470	463	424	427	467	440	473	454	468	432	439	471	447	466
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+			+		+		+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Carcinoma																									X
Fibroadenoma														X				X	X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma						X																			
Squamous cell carcinoma																									
Subcutaneous tissue, lipoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Squamous cell carcinoma, metastatic, skin																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye									+											+					+
Zymbal's gland									+																
Carcinoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X											X			X		X	X	X			X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	643	666	669	667	674	685	685	693	703	703	703	708	727	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	453	451	459	442	444	456	476	475	446	452	480	462	479	422	423	426	438	441	443	445	457	460	461	465	474	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+																					+		7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Fibroadenoma					X	X			X	X			X													8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Squamous cell carcinoma				X																						1
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle				+																						1
Squamous cell carcinoma, metastatic, skin				X																						1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye									+																	4
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X			X													X					X		13

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	3/50 (6%)	0/50 (0%)	1/50 (2%)	2/49 (4%)
Adjusted rate[b]	9.4%	0.0%	4.5%	11.0%
Terminal rate[c]	2/28 (7%)	0/24 (0%)	1/22 (5%)	1/12 (8%)
First incidence (days)	591	–[e]	729 (T)	617
Life table test[d]	P=0.484	P=0.146N	P=0.384N	P=0.641
Logistic regression test[d]	P=0.610N	P=0.127N	P=0.330N	P=0.556N
Cochran-Armitage test[d]	P=0.563N			
Fisher exact test[d]		P=0.121N	P=0.309N	P=0.510N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	2/49 (4%)
Adjusted rate	9.4%	4.2%	6.9%	11.0%
Terminal rate	2/28 (7%)	1/24 (4%)	1/22 (5%)	1/12 (8%)
First incidence (days)	591	729 (T)	565	617
Life table test	P=0.498	P=0.355N	P=0.587N	P=0.641
Logistic regression test	P=0.542N	P=0.327N	P=0.512N	P=0.556N
Cochran-Armitage test	P=0.509N			
Fisher exact test		P=0.309N	P=0.500N	P=0.510N
Clitoral Gland: Adenoma				
Overall rate	4/49 (8%)	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rate	13.1%	17.9%	18.2%	7.3%
Terminal rate	2/27 (7%)	3/24 (13%)	4/22 (18%)	0/12 (0%)
First incidence (days)	645	618	729 (T)	597
Life table test	P=0.506N	P=0.431	P=0.550	P=0.571N
Logistic regression test	P=0.288N	P=0.476	P=0.611	P=0.372N
Cochran-Armitage test	P=0.213N			
Fisher exact test		P=0.513	P=0.631N	P=0.329N
Clitoral Gland: Carcinoma				
Overall rate	3/49 (6%)	2/50 (4%)	6/50 (12%)	4/50 (8%)
Adjusted rate	10.6%	6.6%	24.4%	21.8%
Terminal rate	2/27 (7%)	1/24 (4%)	4/22 (18%)	1/12 (8%)
First incidence (days)	723	591	699	610
Life table test	P=0.073	P=0.548N	P=0.162	P=0.192
Logistic regression test	P=0.193	P=0.521N	P=0.198	P=0.354
Cochran-Armitage test	P=0.317			
Fisher exact test		P=0.490N	P=0.254	P=0.511
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	7/49 (14%)	7/50 (14%)	10/50 (20%)	6/50 (12%)
Adjusted rate	22.8%	23.8%	41.2%	27.5%
Terminal rate	4/27 (15%)	4/24 (17%)	8/22 (36%)	1/12 (8%)
First incidence (days)	645	591	699	597
Life table test	P=0.177	P=0.525	P=0.176	P=0.321
Logistic regression test	P=0.475	P=0.583	P=0.237	P=0.615
Cochran-Armitage test	P=0.459N			
Fisher exact test		P=0.597N	P=0.314	P=0.484N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
Mammary Gland: Fibroadenoma				
Overall rate	12/50 (24%)	14/50 (28%)	11/50 (22%)	8/50 (16%)
Adjusted rate	32.2%	46.5%	40.8%	32.6%
Terminal rate	4/28 (14%)	9/24 (38%)	7/22 (32%)	0/12 (0%)
First incidence (days)	589	533	652	610
Life table test	P=0.468	P=0.292	P=0.524	P=0.556
Logistic regression test	P=0.216N	P=0.353	P=0.543N	P=0.066N
Cochran-Armitage test	P=0.132N			
Fisher exact test		P=0.410	P=0.500N	P=0.227N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	14/50 (28%)	14/50 (28%)	11/50 (22%)	9/50 (18%)
Adjusted rate	37.8%	46.5%	40.8%	35.1%
Terminal rate	6/28 (21%)	9/24 (38%)	7/22 (32%)	0/12 (0%)
First incidence (days)	589	533	652	610
Life table test	P=0.484	P=0.437	P=0.497N	P=0.558
Logistic regression test	P=0.187N	P=0.522	P=0.359N	P=0.049N
Cochran-Armitage test	P=0.109N			
Fisher exact test		P=0.588N	P=0.322N	P=0.171N
Mammary Gland: Carcinoma				
Overall rate	6/50 (12%)	5/50 (10%)	1/50 (2%)	1/50 (2%)
Adjusted rate	18.9%	18.4%	4.2%	3.8%
Terminal rate	3/28 (11%)	3/24 (13%)	0/22 (0%)	0/12 (0%)
First incidence (days)	625	646	708	636
Life table test	P=0.083N	P=0.588N	P=0.098N	P=0.226N
Logistic regression test	P=0.030N	P=0.557N	P=0.071N	P=0.091N
Cochran-Armitage test	P=0.019N			
Fisher exact test		P=0.500N	P=0.056N	P=0.056N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	8/50 (16%)	5/50 (10%)	3/50 (6%)	2/50 (4%)
Adjusted rate	25.4%	18.4%	10.7%	7.4%
Terminal rate	5/28 (18%)	3/24 (13%)	0/22 (0%)	0/12 (0%)
First incidence (days)	625	646	694	631
Life table test	P=0.145N	P=0.371N	P=0.169N	P=0.255N
Logistic regression test	P=0.013N	P=0.329N	P=0.126N	P=0.085N
Cochran-Armitage test	P=0.027N			
Fisher exact test		P=0.277N	P=0.100N	P=0.046N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	17/50 (34%)	16/50 (32%)	12/50 (24%)	10/50 (20%)
Adjusted rate	46.3%	51.8%	43.3%	37.6%
Terminal rate	9/28 (32%)	10/24 (42%)	7/22 (32%)	0/12 (0%)
First incidence (days)	589	533	652	610
Life table test	P=0.516N	P=0.489	P=0.374N	P=0.558N
Logistic regression test	P=0.038N	P=0.587	P=0.213N	P=0.026N
Cochran-Armitage test	P=0.051N			
Fisher exact test		P=0.500N	P=0.189N	P=0.088N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
Oral Cavity (Tongue, Pharynx, or Tooth): Squamous Cell Papilloma				
Overall rate	0/50 (0%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	4.0%	0.0%	5.7%
Terminal rate	0/28 (0%)	0/24 (0%)	0/22 (0%)	0/12 (0%)
First incidence (days)	–	727	–	597
Life table test	P=0.098	P=0.477	–	P=0.216
Logistic regression test	P=0.139	P=0.480	–	P=0.254
Cochran-Armitage test	P=0.140			
Fisher exact test		P=0.500	–	P=0.247
Oral Cavity (Tongue, Pharynx, or Tooth): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	2/50 (4%)
Adjusted rate	0.0%	7.4%	3.0%	5.7%
Terminal rate	0/28 (0%)	0/24 (0%)	0/22 (0%)	0/12 (0%)
First incidence (days)	–	703	651	597
Life table test	P=0.163	P=0.224	P=0.506	P=0.216
Logistic regression test	P=0.239	P=0.217	P=0.502	P=0.254
Cochran-Armitage test	P=0.245			
Fisher exact test		P=0.247	P=0.500	P=0.247
Pancreatic Islets: Adenoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/48 (8%)	1/50 (2%)
Adjusted rate	3.4%	4.0%	18.0%	4.2%
Terminal rate	0/28 (0%)	0/24 (0%)	3/21 (14%)	0/12 (0%)
First incidence (days)	723	727	724	666
Life table test	P=0.261	P=0.735	P=0.114	P=0.637
Logistic regression test	P=0.353	P=0.742	P=0.120	P=0.721
Cochran-Armitage test	P=0.524			
Fisher exact test		P=0.753N	P=0.168	P=0.753N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	4/48 (8%)	1/50 (2%)
Adjusted rate	6.9%	4.0%	18.0%	4.2%
Terminal rate	1/28 (4%)	0/24 (0%)	3/21 (14%)	0/12 (0%)
First incidence (days)	723	727	724	666
Life table test	P=0.404	P=0.543N	P=0.226	P=0.714N
Logistic regression test	P=0.510	P=0.535N	P=0.241	P=0.615N
Cochran-Armitage test	P=0.502N			
Fisher exact test		P=0.500N	P=0.319	P=0.500N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	30/50 (60%)	29/50 (58%)	26/49 (53%)	27/49 (55%)
Adjusted rate	78.2%	79.6%	73.3%	91.8%
Terminal rate	20/28 (71%)	17/24 (71%)	13/22 (59%)	10/12 (83%)
First incidence (days)	524	424	377	576
Life table test	P=0.026	P=0.377	P=0.505	P=0.023
Logistic regression test	P=0.453N	P=0.546	P=0.417N	P=0.575
Cochran-Armitage test	P=0.328N			
Fisher exact test		P=0.500N	P=0.311N	P=0.386N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	31/50 (62%)	30/50 (60%)	27/49 (55%)	28/49 (57%)
Adjusted rate	78.9%	80.2%	74.4%	92.0%
Terminal rate	20/28 (71%)	17/24 (71%)	13/22 (59%)	10/12 (83%)
First incidence (days)	524	424	377	555
Life table test	P=0.026	P=0.374	P=0.499	P=0.024
Logistic regression test	P=0.446N	P=0.547	P=0.425N	P=0.578N
Cochran-Armitage test	P=0.329N			
Fisher exact test		P=0.500N	P=0.311N	P=0.387N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	7.1%	10.8%	0.0%	0.0%
Terminal rate	2/28 (7%)	2/24 (8%)	0/22 (0%)	0/12 (0%)
First incidence (days)	729 (T)	610	–	–
Life table test	P=0.146N	P=0.441	P=0.292N	P=0.438N
Logistic regression test	P=0.096N	P=0.464	P=0.292N	P=0.438N
Cochran-Armitage test	P=0.073N			
Fisher exact test		P=0.500	P=0.247N	P=0.247N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	2/50 (4%)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted rate	7.1%	14.9%	2.4%	0.0%
Terminal rate	2/28 (7%)	3/24 (13%)	0/22 (0%)	0/12 (0%)
First incidence (days)	729 (T)	610	562	–
Life table test	P=0.181N	P=0.277	P=0.564N	P=0.438N
Logistic regression test	P=0.103N	P=0.297	P=0.513N	P=0.438N
Cochran-Armitage test	P=0.086N			
Fisher exact test		P=0.339	P=0.500N	P=0.247N
Thyroid Gland (C-cell): Adenoma				
Overall rate	7/50 (14%)	4/50 (8%)	6/50 (12%)	9/50 (18%)
Adjusted rate	23.5%	12.4%	20.1%	38.2%
Terminal rate	6/28 (21%)	2/24 (8%)	2/22 (9%)	1/12 (8%)
First incidence (days)	625	430	575	610
Life table test	P=0.037	P=0.345N	P=0.599	P=0.070
Logistic regression test	P=0.178	P=0.278N	P=0.559N	P=0.251
Cochran-Armitage test	P=0.217			
Fisher exact test		P=0.262N	P=0.500N	P=0.393
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	4/50 (8%)	6/50 (12%)	9/50 (18%)
Adjusted rate	27.0%	12.4%	20.1%	38.2%
Terminal rate	7/28 (25%)	2/24 (8%)	2/22 (9%)	1/12 (8%)
First incidence (days)	625	430	575	610
Life table test	P=0.059	P=0.251N	P=0.529N	P=0.099
Logistic regression test	P=0.247	P=0.196N	P=0.448N	P=0.328
Cochran-Armitage test	P=0.300			
Fisher exact test		P=0.178N	P=0.387N	P=0.500

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
Uterus: Stromal Polyp				
Overall rate	11/50 (22%)	5/50 (10%)	7/50 (14%)	6/50 (12%)
Adjusted rate	35.7%	18.2%	23.5%	21.4%
Terminal rate	9/28 (32%)	3/24 (13%)	3/22 (14%)	1/12 (8%)
First incidence (days)	547	645	468	597
Life table test	P=0.553N	P=0.145N	P=0.373N	P=0.546N
Logistic regression test	P=0.224N	P=0.111N	P=0.259N	P=0.203N
Cochran-Armitage test	P=0.180N			
Fisher exact test		P=0.086N	P=0.218N	P=0.143N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	11/50 (22%)	5/50 (10%)	7/50 (14%)	6/50 (12%)
Adjusted rate	35.7%	18.2%	23.5%	21.4%
Terminal rate	9/28 (32%)	3/24 (13%)	3/22 (14%)	1/12 (8%)
First incidence (days)	547	645	468	597
Life table test	P=0.553N	P=0.145N	P=0.373N	P=0.546N
Logistic regression test	P=0.224N	P=0.111N	P=0.259N	P=0.203N
Cochran-Armitage test	P=0.180N			
Fisher exact test		P=0.086N	P=0.218N	P=0.143N
All Organs: Mononuclear Cell Leukemia				
Overall rate	22/50 (44%)	20/50 (40%)	18/50 (36%)	13/50 (26%)
Adjusted rate	54.4%	49.9%	52.7%	42.7%
Terminal rate	11/28 (39%)	5/24 (21%)	8/22 (36%)	2/12 (17%)
First incidence (days)	524	232	468	476
Life table test	P=0.377N	P=0.548	P=0.506N	P=0.429N
Logistic regression test	P=0.013N	P=0.396N	P=0.397N	P=0.044N
Cochran-Armitage test	P=0.031N			
Fisher exact test		P=0.420N	P=0.270N	P=0.046N
All Organs: Benign Neoplasms				
Overall rate	44/50 (88%)	42/50 (84%)	38/50 (76%)	38/50 (76%)
Adjusted rate	97.8%	95.3%	92.5%	94.6%
Terminal rate	27/28 (96%)	22/24 (92%)	19/22 (86%)	10/12 (83%)
First incidence (days)	428	424	377	206
Life table test	P=0.026	P=0.355	P=0.504	P=0.027
Logistic regression test	P=0.085N	P=0.539N	P=0.220N	P=0.143N
Cochran-Armitage test	P=0.064N			
Fisher exact test		P=0.387N	P=0.096N	P=0.096N
All Organs: Malignant Neoplasms				
Overall rate	33/50 (66%)	31/50 (62%)	27/50 (54%)	21/50 (42%)
Adjusted rate	72.8%	73.1%	69.4%	64.3%
Terminal rate	16/28 (57%)	13/24 (54%)	11/22 (50%)	4/12 (33%)
First incidence (days)	226	232	321	476
Life table test	P=0.473N	P=0.464	P=0.476N	P=0.534N
Logistic regression test	P=0.006N	P=0.383N	P=0.150N	P=0.011N
Cochran-Armitage test	P=0.006N			
Fisher exact test		P=0.418N	P=0.154N	P=0.013N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
All Organs: Benign or Malignant Neoplasms				
Overall rate	48/50 (96%)	47/50 (94%)	44/50 (88%)	47/50 (94%)
Adjusted rate	100.0%	95.9%	97.8%	100.0%
Terminal rate	28/28 (100%)	22/24 (92%)	21/22 (95%)	12/12 (100%)
First incidence (days)	226	232	321	206
Life table test	P=0.003	P=0.297	P=0.357	P=0.003
Logistic regression test	P=0.431N	P=0.525N	P=0.269N	P=0.550N
Cochran-Armitage test	P=0.389N			
Fisher exact test		P=0.500N	P=0.134N	P=0.500N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, pancreatic islets, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B4
Historical Incidence of Renal Tubule Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Chlorinated and Chloraminated Water	0/50	0/50	0/50
t-Butyl Alcohol	0/50	0/50	0/50
Overall Historical Incidence			
Total	0/278 (0.0%)	0/278 (0.0%)	0/278 (0.0%)

[a] Data as of 31 March 1993

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	15	18	21	35
Natural deaths	7	8	7	3
Survivors				
Terminal sacrifice	28	24	22	12
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan			2 (20%)	1 (10%)
Intestine large, rectum	(9)	(10)	(10)	(10)
Parasite metazoan	3 (33%)	5 (50%)	1 (10%)	
Intestine large, cecum	(10)	(10)	(10)	(10)
Parasite metazoan		1 (10%)		1 (10%)
Liver	(10)	(10)	(10)	(10)
Basophilic focus	9 (90%)	6 (60%)	7 (70%)	6 (60%)
Clear cell focus	1 (10%)			
Granuloma	5 (50%)	4 (40%)	3 (30%)	4 (40%)
Hepatodiaphragmatic nodule	4 (40%)	1 (10%)	3 (30%)	4 (40%)
Hyperplasia, focal		1 (10%)	2 (20%)	
Hyperplasia, lymphoid	1 (10%)			
Inflammation, subacute	5 (50%)	5 (50%)	2 (20%)	5 (50%)
Mixed cell focus		1 (10%)	1 (10%)	
Bile duct, hyperplasia	1 (10%)	3 (30%)	6 (60%)	5 (50%)
Mesentery	(1)			
Accessory spleen	1 (100%)			
Pancreas	(10)	(10)	(10)	(10)
Atrophy	2 (20%)	4 (40%)	2 (20%)	3 (30%)
Cyst				1 (10%)
Salivary glands	(10)	(10)	(10)	(10)
Atrophy		1 (10%)		
Stomach, glandular	(10)	(10)	(10)	(10)
Epithelium, dilatation	2 (20%)	3 (30%)	1 (10%)	3 (30%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy	2 (20%)		2 (20%)	

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
15-Month Interim Evaluation (continued)				
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	2 (20%)	2 (20%)	1 (10%)	3 (30%)
Angiectasis	5 (50%)	2 (20%)	6 (60%)	2 (20%)
Hyperplasia, focal	3 (30%)	5 (50%)	2 (20%)	3 (30%)
Vacuolization cytoplasmic, focal				1 (10%)
Adrenal medulla	(10)	(10)	(10)	(10)
Angiectasis			2 (20%)	
Islets, pancreatic	(10)	(10)	(10)	(10)
Hyperplasia	2 (20%)		1 (10%)	
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, angiectasis	1 (10%)	2 (20%)	2 (20%)	
Pars distalis, cyst	5 (50%)	5 (50%)	6 (60%)	5 (50%)
Pars distalis, hyperplasia	3 (30%)	3 (30%)	4 (40%)	4 (40%)
Pars intermedia, angiectasis	1 (10%)			1 (10%)
Pars intermedia, cyst	1 (10%)	1 (10%)		
Thyroid gland	(9)	(10)	(10)	(10)
C-cell, hyperplasia	2 (22%)			1 (10%)
Follicle, cyst			1 (10%)	1 (10%)
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Hyperplasia	1 (10%)	1 (10%)		
Inflammation, chronic	1 (10%)	2 (20%)	1 (10%)	
Inflammation, suppurative		1 (10%)		
Ovary	(10)	(10)	(10)	(10)
Cyst	1 (10%)	2 (20%)	1 (10%)	2 (20%)
Uterus	(10)	(10)	(10)	(10)
Hydrometra	1 (10%)	1 (10%)		4 (40%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Myelofibrosis	2 (20%)	4 (40%)	2 (20%)	2 (20%)
Lymph node			(3)	
Pancreatic, hemorrhage			3 (100%)	
Pancreatic, pigmentation			1 (33%)	
Lymph node, mandibular	(10)	(10)	(10)	(10)
Ectasia				1 (10%)
Hemorrhage				2 (20%)
Hyperplasia, plasma cell	1 (10%)		1 (10%)	2 (20%)
Spleen	(10)	(10)	(10)	(10)
Pigmentation	10 (100%)	10 (100%)	9 (90%)	9 (90%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
15-Month Interim Evaluation (continued)				
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Hyperplasia, cystic	3 (30%)	5 (50%)	5 (50%)	6 (60%)
Skin	(10)	(10)	(10)	(10)
Acanthosis	1 (10%)			2 (20%)
Exudate				1 (10%)
Ulcer				1 (10%)
Musculoskeletal System				
Bone	(10)	(10)	(10)	(10)
Developmental malformation		1 (10%)		
Nervous System				
Brain	(10)	(10)	(10)	(10)
Developmental malformation		1 (10%)		
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid	1 (10%)			
Infiltration cellular, histiocyte	1 (10%)	2 (20%)	3 (30%)	
Inflammation, subacute		1 (10%)	1 (10%)	
Bronchiole, epithelium, hyperplasia			1 (10%)	
Nose	(10)	(10)	(10)	(10)
Exudate		1 (10%)	1 (10%)	
Foreign body		1 (10%)		
Fungus			1 (10%)	
Mucosa, hyperplasia			1 (10%)	
Mucosa, metaplasia, squamous			1 (10%)	
Special Senses System				
Eye				(1)
Cataract				1 (100%)
Retina, atrophy				1 (100%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Nephropathy	10 (100%)	10 (100%)	10 (100%)	10 (100%)
System Examined With No Lesions Observed				
General Body System				

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Ulcer			1 (2%)	
Mucosa, hyperplasia			1 (2%)	
Intestine large, colon	(50)	(50)	(49)	(50)
Parasite metazoan	5 (10%)	3 (6%)	1 (2%)	4 (8%)
Intestine large, rectum	(50)	(49)	(49)	(50)
Edema		1 (2%)		
Parasite metazoan	8 (16%)	3 (6%)	2 (4%)	6 (12%)
Ulcer				1 (2%)
Intestine large, cecum	(50)	(49)	(49)	(50)
Dilatation	1 (2%)	1 (2%)	1 (2%)	
Edema		1 (2%)		
Parasite metazoan	1 (2%)		1 (2%)	
Intestine small, duodenum	(50)	(50)	(49)	(50)
Erosion			3 (6%)	1 (2%)
Intestine small, jejunum	(50)	(49)	(49)	(50)
Dilatation	1 (2%)			
Inflammation, subacute	1 (2%)			
Mucosa, hyperplasia, diffuse			1 (2%)	
Intestine small, ileum	(50)	(49)	(49)	(50)
Inflammation, subacute	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis	6 (12%)	5 (10%)	6 (12%)	4 (8%)
Basophilic focus	36 (72%)	33 (66%)	29 (58%)	40 (80%)
Clear cell focus	9 (18%)	5 (10%)	4 (8%)	2 (4%)
Congestion		1 (2%)		
Eosinophilic focus			2 (4%)	1 (2%)
Granuloma	8 (16%)	9 (18%)	10 (20%)	13 (26%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Hepatodiaphragmatic nodule	10 (20%)	15 (30%)	16 (32%)	11 (22%)
Hyperplasia, focal	9 (18%)	10 (20%)	12 (24%)	5 (10%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)		1 (2%)
Inflammation, subacute	5 (10%)	11 (22%)	2 (4%)	1 (2%)
Mixed cell focus	7 (14%)	8 (16%)	5 (10%)	2 (4%)
Thrombosis				1 (2%)
Bile duct, cyst	3 (6%)	1 (2%)		1 (2%)
Bile duct, hyperplasia	13 (26%)	19 (38%)	10 (20%)	12 (24%)
Centrilobular, atrophy	7 (14%)	9 (18%)	7 (14%)	7 (14%)
Centrilobular, necrosis		1 (2%)	2 (4%)	1 (2%)
Hepatocyte, vacuolization cytoplasmic	10 (20%)	13 (26%)	12 (24%)	7 (14%)
Kupffer cell, hyperplasia			1 (2%)	2 (4%)
Kupffer cell, pigmentation	3 (6%)	9 (18%)	5 (10%)	5 (10%)
Lobules, necrosis	4 (8%)	4 (8%)	2 (4%)	7 (14%)
Mesentery	(8)	(6)	(8)	(6)
Accessory spleen				1 (17%)
Fat, necrosis	7 (88%)	6 (100%)	6 (75%)	5 (83%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(50)	(50)	(49)	(50)
Atrophy	15 (30%)	25 (50%)	21 (43%)	20 (40%)
Cyst		1 (2%)		2 (4%)
Ectopic liver				1 (2%)
Hyperplasia, lymphoid			1 (2%)	
Acinar cell, cytoplasmic alteration	4 (8%)	1 (2%)	8 (16%)	9 (18%)
Acinar cell, hyperplasia, focal		2 (4%)	1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Inflammation, suppurative			1 (2%)	
Acinar cell, cytoplasmic alteration	1 (2%)	4 (8%)	3 (6%)	5 (10%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	4 (8%)	5 (10%)	8 (16%)	2 (4%)
Erosion	1 (2%)	3 (6%)	1 (2%)	
Fibrosis			4 (8%)	2 (4%)
Inflammation, subacute	1 (2%)			
Perforation			3 (6%)	
Ulcer	5 (10%)	3 (6%)	9 (18%)	9 (18%)
Mucosa, hyperplasia	8 (16%)	2 (4%)	16 (32%)	12 (24%)
Stomach, glandular	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Edema	2 (4%)	3 (6%)	4 (8%)	
Erosion	5 (10%)	4 (8%)	2 (4%)	8 (16%)
Inflammation, chronic				1 (2%)
Mineralization				1 (2%)
Ulcer	2 (4%)	1 (2%)	4 (8%)	3 (6%)
Epithelium, dilatation			1 (2%)	2 (4%)
Tongue		(1)	(1)	(3)
Hyperplasia				1 (33%)
Cardiovascular System				
Blood vessel			(1)	
Fibrosis			1 (100%)	
Inflammation, chronic active			1 (100%)	
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	16 (32%)	15 (30%)	21 (42%)	12 (24%)
Thrombosis		1 (2%)	3 (6%)	1 (2%)
Myocardium, inflammation, chronic		1 (2%)		2 (4%)
Myocardium, mineralization				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	9 (18%)	9 (18%)	6 (12%)	12 (24%)
Angiectasis	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Atrophy	2 (4%)			
Basophilic focus	1 (2%)			1 (2%)
Congestion	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Cyst		1 (2%)		
Hematopoietic cell proliferation	4 (8%)	3 (6%)	4 (8%)	
Hemorrhage		2 (4%)		
Hyperplasia, diffuse				2 (4%)
Hyperplasia, focal	3 (6%)	9 (18%)	6 (12%)	6 (12%)
Hypertrophy, focal	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Metaplasia, osseous	1 (2%)			
Necrosis	1 (2%)		1 (2%)	
Pigmentation	2 (4%)	2 (4%)	1 (2%)	
Vacuolization cytoplasmic, diffuse	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Vacuolization cytoplasmic, focal	14 (28%)	12 (24%)	15 (30%)	12 (24%)
Adrenal medulla	(50)	(50)	(50)	(49)
Hyperplasia	4 (8%)	10 (20%)	9 (18%)	4 (8%)
Islets, pancreatic	(50)	(50)	(48)	(50)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Parathyroid gland	(47)	(50)	(47)	(50)
Fibrosis			1 (2%)	
Hyperplasia	1 (2%)		1 (2%)	1 (2%)
Pituitary gland	(50)	(50)	(49)	(49)
Hypertrophy, focal			1 (2%)	
Pigmentation	2 (4%)	2 (4%)	3 (6%)	6 (12%)
Pars distalis, angiectasis	10 (20%)	8 (16%)	9 (18%)	6 (12%)
Pars distalis, atrophy	1 (2%)			
Pars distalis, cyst	18 (36%)	14 (28%)	17 (35%)	14 (29%)
Pars distalis, hyperplasia	13 (26%)	8 (16%)	17 (35%)	14 (29%)
Pars distalis, infiltration cellular, histiocyte				1 (2%)
Pars intermedia, angiectasis	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Pars intermedia, cyst	4 (8%)	5 (10%)	2 (4%)	3 (6%)
Pars intermedia, hyperplasia			1 (2%)	
Pars intermedia, hypertrophy, focal			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Degeneration, cystic			1 (2%)	2 (4%)
Ultimobranchial cyst	1 (2%)	3 (6%)	2 (4%)	3 (6%)
C-cell, hyperplasia	19 (38%)	17 (34%)	13 (26%)	12 (24%)
Follicle, cyst	1 (2%)	2 (4%)	1 (2%)	5 (10%)
General Body System				
None				

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
2-Year Study (continued)				
Genital System				
Clitoral gland	(49)	(50)	(50)	(50)
Ectasia	1 (2%)	2 (4%)	1 (2%)	
Hyperplasia	3 (6%)	3 (6%)	4 (8%)	4 (8%)
Inflammation, chronic	7 (14%)	1 (2%)	2 (4%)	2 (4%)
Inflammation, suppurative	4 (8%)	1 (2%)		1 (2%)
Necrosis	1 (2%)			
Ovary	(50)	(50)	(50)	(50)
Cyst	11 (22%)	12 (24%)	16 (32%)	15 (30%)
Mineralization		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Hydrometra	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, cystic	2 (4%)	2 (4%)	5 (10%)	1 (2%)
Inflammation, suppurative			1 (2%)	
Pigmentation	1 (2%)		1 (2%)	3 (6%)
Prolapse			1 (2%)	
Endometrium, fibrosis			1 (2%)	
Vagina	(3)	(3)	(6)	(6)
Cyst				1 (17%)
Exudate		1 (33%)	2 (33%)	1 (17%)
Hyperplasia				1 (17%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Congestion			1 (2%)	1 (2%)
Hypercellularity		2 (4%)	3 (6%)	1 (2%)
Myelofibrosis	2 (4%)	7 (14%)	1 (2%)	3 (6%)
Lymph node	(14)	(15)	(9)	(7)
Mediastinal, hemorrhage	2 (14%)	1 (7%)	5 (56%)	
Mediastinal, hyperplasia, histiocytic	1 (7%)			
Mediastinal, pigmentation	2 (14%)	3 (20%)	3 (33%)	
Pancreatic, hemorrhage		1 (7%)		
Pancreatic, hyperplasia, lymphoid	1 (7%)			
Pancreatic, pigmentation	1 (7%)			
Renal, hemorrhage		1 (7%)		
Renal, pigmentation		1 (7%)		
Lymph node, mandibular	(50)	(49)	(50)	(49)
Ectasia	4 (8%)	5 (10%)	8 (16%)	1 (2%)
Hemorrhage	1 (2%)	2 (4%)	3 (6%)	
Hyperplasia, histiocytic	1 (2%)			
Hyperplasia, lymphoid	3 (6%)	3 (6%)	1 (2%)	4 (8%)
Hyperplasia, plasma cell	6 (12%)	8 (16%)	9 (18%)	10 (20%)
Infiltration cellular, mast cell		1 (2%)		
Pigmentation	3 (6%)		1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mesenteric	(50)	(49)	(50)	(50)
Ectasia	1 (2%)			1 (2%)
Hemorrhage	3 (6%)	3 (6%)	8 (16%)	3 (6%)
Hyperplasia, histiocytic	1 (2%)			
Hyperplasia, lymphoid	2 (4%)	5 (10%)	2 (4%)	
Hyperplasia, plasma cell	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, mast cell		1 (2%)	1 (2%)	1 (2%)
Inflammation, suppurative	1 (2%)			
Pigmentation	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Congestion	1 (2%)			
Developmental malformation	1 (2%)	1 (2%)	1 (2%)	
Fibrosis	4 (8%)	5 (10%)	3 (6%)	5 (10%)
Hematopoietic cell proliferation	19 (38%)	19 (38%)	17 (34%)	16 (32%)
Infiltration cellular, histiocyte	1 (2%)			
Necrosis	2 (4%)			
Pigmentation	34 (68%)	32 (64%)	33 (66%)	35 (70%)
Lymphoid follicle, atrophy	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Red pulp, atrophy			1 (2%)	2 (4%)
Thymus	(48)	(47)	(49)	(48)
Congestion	1 (2%)	1 (2%)	2 (4%)	
Cyst	1 (2%)	1 (2%)		1 (2%)
Ectopic parathyroid gland				1 (2%)
Hemorrhage			2 (4%)	1 (2%)
Integumentary System				
Mammary gland	(50)	(49)	(50)	(50)
Hyperplasia, cystic	38 (76%)	42 (86%)	40 (80%)	45 (90%)
Hyperplasia, lobular	5 (10%)	7 (14%)	5 (10%)	6 (12%)
Skin	(50)	(50)	(49)	(50)
Acanthosis	2 (4%)			2 (4%)
Exudate	2 (4%)			
Inflammation, subacute	1 (2%)			
Ulcer				1 (2%)
Subcutaneous tissue, edema		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy		1 (2%)	4 (8%)	5 (10%)
Calvarium, osteopetrosis	20 (40%)	9 (18%)	11 (22%)	10 (20%)
Femur, osteopetrosis	12 (24%)	7 (14%)	4 (8%)	8 (16%)
Sternum, osteopetrosis	12 (24%)	8 (16%)	4 (8%)	8 (16%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
2-Year Study (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	16 (32%)	13 (26%)	12 (24%)	10 (20%)
Developmental malformation	1 (2%)			1 (2%)
Hemorrhage				2 (4%)
Hydrocephalus	3 (6%)	6 (12%)	1 (2%)	4 (8%)
Mineralization			1 (2%)	
Necrosis				1 (2%)
Spinal cord			(1)	
Hemorrhage			1 (100%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)	4 (8%)	4 (8%)	1 (2%)
Edema		3 (6%)		
Foreign body	1 (2%)			
Hemorrhage	1 (2%)	2 (4%)	2 (4%)	
Infiltration cellular, histiocyte	23 (46%)	17 (34%)	19 (38%)	17 (34%)
Inflammation, subacute	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, suppurative	1 (2%)			
Leukocytosis			1 (2%)	
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	4 (8%)	2 (4%)	4 (8%)	2 (4%)
Nose	(50)	(50)	(50)	(50)
Exudate	7 (14%)	10 (20%)	14 (28%)	15 (30%)
Foreign body	3 (6%)	2 (4%)	5 (10%)	7 (14%)
Fungus	4 (8%)	2 (4%)	4 (8%)	9 (18%)
Glands, hyperplasia	1 (2%)	1 (2%)		
Mucosa, hyperplasia	7 (14%)	4 (8%)	7 (14%)	8 (16%)
Mucosa, metaplasia, squamous	4 (8%)	3 (6%)	3 (6%)	7 (14%)
Mucosa, necrosis			1 (2%)	2 (4%)
Trachea	(50)	(50)	(50)	(50)
Mucosa, hyperplasia	1 (2%)			
Special Senses System				
Eye	(2)	(5)	(5)	(4)
Cataract	2 (100%)	4 (80%)	5 (100%)	3 (75%)
Hemorrhage				1 (25%)
Retina, atrophy	2 (100%)	4 (80%)	5 (100%)	3 (75%)
Lacrimal gland			(1)	
Ectopic harderian			1 (100%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Infarct	1 (2%)			
Inflammation, suppurative	2 (4%)	3 (6%)	13 (26%)	17 (34%)
Mineralization	49 (98%)	50 (100%)	50 (100%)	50 (100%)
Nephropathy	48 (96%)	47 (94%)	48 (96%)	50 (100%)
Interstitial tissue, pigmentation	1 (2%)	1 (2%)		1 (2%)
Renal tubule, cytoplasmic alteration	5 (10%)	4 (8%)	3 (6%)	4 (8%)
Renal tubule, hyperplasia				1 (2%)
Renal tubule, pigmentation	10 (20%)	12 (24%)	6 (12%)	5 (10%)
Transitional epithelium, hyperplasia			3 (6%)	17 (34%)
Urinary bladder	(50)	(50)	(50)	(50)
Dilatation			2 (4%)	
Hemorrhage			2 (4%)	
Inflammation, suppurative	1 (2%)			
Mineralization				1 (2%)
Mucosa, hyperplasia	1 (2%)	1 (2%)	1 (2%)	

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF *t*-BUTYL ALCOHOL

TABLE C1 Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 156

TABLE C2 Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 160

TABLE C3 Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 190

TABLE C4a Historical Incidence of Liver Neoplasms in Untreated Male $B6C3F_1$ Mice 195

TABLE C4b Historical Incidence of Thyroid Gland Follicullar Cell Neoplasms in Untreated Male $B6C3F_1$ Mice 195

TABLE C5 Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 196

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Disposition Summary				
Animals initially in study	60	60	60	60
Early deaths				
Accidental deaths		2	1	
Moribund	20	14	19	21
Natural deaths	13	8	6	22
Survivors				
Terminal sacrifice	27	36	34	17
Animals examined microscopically	60	60	60	60
Alimentary System				
Gallbladder	(55)	(57)	(59)	(54)
Histiocytic sarcoma	1 (2%)			
Intestine small, duodenum	(56)	(56)	(57)	(56)
Polyp adenomatous				1 (2%)
Intestine small, jejunum	(56)	(56)	(57)	(55)
Adenocarcinoma	1 (2%)		2 (4%)	
Hemangioma		1 (2%)		
Polyp adenomatous			1 (2%)	
Intestine small, ileum	(56)	(56)	(57)	(55)
Polyp adenomatous		1 (2%)		
Liver	(59)	(60)	(59)	(59)
Cholangiocarcinoma	1 (2%)	1 (2%)		
Hemangioma		2 (3%)		
Hemangiosarcoma	3 (5%)	5 (8%)	2 (3%)	
Hepatoblastoma	2 (3%)	2 (3%)	4 (7%)	2 (3%)
Hepatoblastoma, multiple				1 (2%)
Hepatocellular carcinoma	14 (24%)	14 (23%)	21 (36%)	14 (24%)
Hepatocellular carcinoma, multiple	11 (19%)	15 (25%)	14 (24%)	5 (8%)
Hepatocellular adenoma	18 (31%)	15 (25%)	22 (37%)	13 (22%)
Hepatocellular adenoma, multiple	21 (36%)	26 (43%)	22 (37%)	13 (22%)
Hepatocellular adenoma, multiple, two	1 (2%)			
Histiocytic sarcoma	2 (3%)		1 (2%)	
Sarcoma, metastatic, mesentery	1 (2%)			
Mesentery	(5)	(6)	(7)	(4)
Hemangiosarcoma		1 (17%)		
Hepatocellular carcinoma, metastatic, liver		1 (17%)		
Histiocytic sarcoma	1 (20%)		1 (14%)	
Sarcoma	1 (20%)			
Pancreas	(58)	(59)	(59)	(57)
Cholangiocarcinoma, metastatic, liver	1 (2%)			
Sarcoma, metastatic, mesentery	1 (2%)			
Stomach, forestomach	(59)	(59)	(59)	(58)
Sarcoma, metastatic, mesentery	1 (2%)			
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma		2 (3%)		
Stomach, glandular	(59)	(59)	(59)	(57)
Sarcoma, metastatic, mesentery	1 (2%)			
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (2%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Cardiovascular System				
Heart	(60)	(60)	(60)	(60)
Pericardium, cholangiocarcinoma, metastatic, liver		1 (2%)		
Endocrine System				
Adrenal cortex	(60)	(60)	(60)	(60)
Adenoma	1 (2%)		2 (3%)	
Sarcoma, metastatic, mesentery	1 (2%)			
Subcapsular, adenoma	3 (5%)	5 (8%)		2 (3%)
Islets, pancreatic	(59)	(59)	(59)	(57)
Adenoma	1 (2%)		1 (2%)	
Carcinoma		1 (2%)		
Pituitary gland	(52)	(57)	(56)	(53)
Pars distalis, adenoma		1 (2%)		
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(60)	(59)	(59)	(57)
Follicular cell, adenoma	1 (2%)		4 (7%)	1 (2%)
Follicular cell, carcinoma				1 (2%)
General Body System				
Tissue NOS	(1)	(1)		
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung	1 (100%)			
Thoracic, sarcoma		1 (100%)		
Genital System				
Epididymis	(60)	(60)	(60)	(60)
Histiocytic sarcoma			2 (3%)	
Testes	(60)	(60)	(60)	(59)
Interstitial cell, adenoma	1 (2%)			
Hematopoietic System				
Bone marrow	(60)	(60)	(60)	(60)
Hemangiosarcoma	1 (2%)	1 (2%)		1 (2%)
Histiocytic sarcoma	1 (2%)			
Lymph node	(9)	(5)	(1)	(1)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	1 (11%)			
Mediastinal, cholangiocarcinoma, metastatic, liver		1 (20%)		
Mediastinal, histiocytic sarcoma	1 (11%)			
Renal, histiocytic sarcoma	1 (11%)			
Lymph node, mandibular	(57)	(59)	(58)	(56)
Histiocytic sarcoma	1 (2%)			
Lymph node, mesenteric	(59)	(58)	(57)	(56)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (2%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Hematopoietic System (continued)				
Spleen	(59)	(59)	(59)	(57)
Hemangioma				1 (2%)
Hemangiosarcoma	1 (2%)	2 (3%)	1 (2%)	1 (2%)
Histiocytic sarcoma	2 (3%)	1 (2%)		
Thymus	(53)	(54)	(55)	(52)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Thymocyte, thymoma malignant			1 (2%)	
Integumentary System				
Skin	(60)	(60)	(60)	(60)
Basal cell adenoma			1 (2%)	
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)		
Subcutaneous tissue, hemangioma		2 (3%)		
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Musculoskeletal System				
Bone	(60)	(60)	(60)	(60)
Osteoma	1 (2%)			
Skeletal muscle	(2)			(1)
Hemangiosarcoma				1 (100%)
Sarcoma, metastatic, mesentery	1 (50%)			
Nervous System				
None				
Respiratory System				
Lung	(60)	(60)	(60)	(60)
Alveolar/bronchiolar adenoma	10 (17%)	6 (10%)	6 (10%)	4 (7%)
Alveolar/bronchiolar adenoma, multiple, two	2 (3%)			
Alveolar/bronchiolar carcinoma	4 (7%)	2 (3%)	3 (5%)	2 (3%)
Carcinoma				1 (2%)
Cholangiocarcinoma, metastatic, liver	1 (2%)			
Hepatoblastoma, metastatic, liver				1 (2%)
Hepatocellular carcinoma, metastatic, liver	4 (7%)	3 (5%)	2 (3%)	3 (5%)
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, mesentery	1 (2%)			
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Mediastinum, hemangiosarcoma	1 (2%)			
Pleura, cholangiocarcinoma, metastatic, liver		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Special Senses System				
Ear			(2)	
Pinna, fibrosarcoma			1 (50%)	
Harderian gland	(10)	(3)	(3)	(1)
Adenoma	8 (80%)	3 (100%)	2 (67%)	1 (100%)
Carcinoma	2 (20%)		1 (33%)	
Urinary System				
Kidney	(60)	(58)	(59)	(57)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Cholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Renal tubule, adenocarcinoma		1 (2%)		1 (2%)
Renal tubule, adenoma	1 (2%)	1 (2%)		
Urinary bladder	(59)	(59)	(58)	(59)
Hemangioma		1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(60)	(60)	(60)	(60)
Histiocytic sarcoma	2 (3%)	1 (2%)	2 (3%)	
Lymphoma malignant mixed	7 (12%)	2 (3%)	5 (8%)	2 (3%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	56	56	56	43
Total primary neoplasms	123	118	119	68
Total animals with benign neoplasms	47	49	50	31
Total benign neoplasms	69	67	62	36
Total animals with malignant neoplasms	41	40	43	27
Total malignant neoplasms	54	51	57	32
Total animals with metastatic neoplasms	8	4	2	4
Total metastatic neoplasms	20	7	2	4

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL

Number of Days on Study	362	461	486	499	498	560	589	616	631	633	636	638	643	647	647	652	652	653	653	673	673	675	675	689	692
Carcass ID Number	020	004	003	015	056	006	016	028	021	010	032	025	042	040	059	014	048	050	051	099	057	024	052	044	019
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A
Histiocytic sarcoma																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	A
Intestine small, duodenum	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	A
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	A
Adenocarcinoma																								X	
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Cholangiocarcinoma																					X				
Hemangiosarcoma											X														
Hepatoblastoma															X										
Hepatocellular carcinoma		X			X			X	X				X			X		X							
Hepatocellular carcinoma, multiple										X										X					
Hepatocellular adenoma					X			X								X	X	X	X	X					
Hepatocellular adenoma, multiple									X				X	X	X								X	X	
Hepatocellular adenoma, multiple, two																									
Histiocytic sarcoma																									
Sarcoma, metastatic, mesentery								X																	
Mesentery								+			+														
Histiocytic sarcoma																									
Sarcoma								X																	
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Cholangiocarcinoma, metastatic, liver																					X				
Sarcoma, metastatic, mesentery								X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Sarcoma, metastatic, mesentery								X																	
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Sarcoma, metastatic, mesentery								X																	
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Tooth	+		+	+				+	+		+		+	+	+	+			+			+	+	+	+
Cardiovascular System																									
Blood vessel		+																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Sarcoma, metastatic, mesentery								X																	
Subcapsular, adenoma																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	702	707	707	707	707	708	709	727	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	054	012	018	037	060	053	049	041	011	007	008	011	013	017	026	027	029	030	031	033	034	035	036	038	039
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Hemangiosarcoma																							X		
Hepatoblastoma	X																								
Hepatocellular carcinoma		X				X	X										X								
Hepatocellular carcinoma, multiple					X				X			X				X					X		X	X	
Hepatocellular adenoma				X			X		X							X	X		X	X		X			
Hepatocellular adenoma, multiple			X					X		X	X		X	X							X		X	X	X
Hepatocellular adenoma, multiple, two																									
Histiocytic sarcoma							X											X							
Sarcoma, metastatic, mesentery																									
Mesentery	+				+		+																		
Histiocytic sarcoma							X																		
Sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver																									
Sarcoma, metastatic, mesentery																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																									
Squamous cell carcinoma					X																				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																									
Squamous cell carcinoma, metastatic, stomach, forestomach					X																				
Tooth	+	+	+	+			+	+	+	+	+	+	+		+	+	+	+	+	+	+		+		+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Sarcoma, metastatic, mesentery																									
Subcapsular, adenoma											X														

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	
Carcass ID Number	055	058	002	005	022	023	043	045	046	047	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	+	+	+	+	55
Histiocytic sarcoma											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	58
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	57
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	56
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	56
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	56
Adenocarcinoma											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	56
Liver	+	+	+	+	+	+	+	+	+	+	59
Cholangiocarcinoma											1
Hemangiosarcoma						X					3
Hepatoblastoma											2
Hepatocellular carcinoma		X	X		X						14
Hepatocellular carcinoma, multiple	X					X					11
Hepatocellular adenoma		X	X				X				18
Hepatocellular adenoma, multiple	X			X		X		X		X	21
Hepatocellular adenoma, multiple, two									X		1
Histiocytic sarcoma											2
Sarcoma, metastatic, mesentery											1
Mesentery											5
Histiocytic sarcoma											1
Sarcoma											1
Pancreas	+	+	+	+	+	+	+	+	+	+	58
Cholangiocarcinoma, metastatic, liver											1
Sarcoma, metastatic, mesentery											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	59
Sarcoma, metastatic, mesentery											1
Squamous cell carcinoma											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Sarcoma, metastatic, mesentery											1
Squamous cell carcinoma, metastatic, stomach, forestomach											1
Tooth	+		+	+	+	+	+	+	+	+	44
Cardiovascular System											
Blood vessel											1
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Sarcoma, metastatic, mesentery											1
Subcapsular, adenoma						X	X				3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	362	461	486	496	498	560	589	616	631	633	636	638	643	647	647	652	652	653	653	673	673	675	675	689	692
Carcass ID Number	020	004	003	015	056	066	061	028	021	010	032	025	042	040	059	014	048	050	051	093	057	024	052	044	019
Endocrine System (continued)																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	M	+	+	+	+	+	M
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS					+																				
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung					X																				
Genital System																									
Coagulating gland									+			+			+							+	+		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland			+	+				+					+	+	+					+	+			+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma										X															
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Histiocytic sarcoma																									
Lymph node			+		+											+			+			+			
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung					X																				
Mediastinal, histiocytic sarcoma																									
Renal, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Hemangiosarcoma											X														
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	M	I	+	+	+	+	+	+	I
Hemangiosarcoma																									
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma							X																		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	702	707	707	707	707	708	709	727	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	054	012	018	037	060	053	049	041	011	007	008	011	013	017	026	027	029	030	031	033	034	035	036	038	039
Endocrine System (continued)																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma								X																	
General Body System																									
Tissue NOS																									
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung																									
Genital System																									
Coagulating gland	+		+	+				+		+		+	+			+	+			+	+	+	+		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+			+		+		+		+	+		+	+		+			+		+	+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma							X																		
Lymph node			+		+		+																+		
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																									
Mediastinal, histiocytic sarcoma							X																		
Renal, histiocytic sarcoma							X																		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Squamous cell carcinoma, metastatic, stomach, forestomach					X																				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma							X											X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Histiocytic sarcoma							X																		
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	
Carcass ID Number	055	058	002	005	022	023	043	045	046	047	Total Tissues/ Tumors
Endocrine System (continued)											
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	55
Pituitary gland	+	+	+	+	+	I	+	+	+	+	52
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Follicular cell, adenoma											1
General Body System											
Tissue NOS											1
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung											1
Genital System											
Coagulating gland		+	+			+	+	+			23
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Preputial gland	+	+			+	+	+	+			27
Prostate	+	+	+	+	+	+	+	+	+	+	60
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	60
Testes	+	+	+	+	+	+	+	+	+	+	60
Interstitial cell, adenoma											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Histiocytic sarcoma											1
Lymph node											9
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung											1
Mediastinal, histiocytic sarcoma											1
Renal, histiocytic sarcoma											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	57
Histiocytic sarcoma											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	59
Histiocytic sarcoma											1
Squamous cell carcinoma, metastatic, stomach, forestomach											1
Spleen	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma											1
Histiocytic sarcoma											2
Thymus	+	+	+	+	+	+	+	+	M	+	53
Hemangiosarcoma											1
Histiocytic sarcoma											1
Integumentary System											
Mammary gland	M	M	M	+	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	60
Subcutaneous tissue, fibrosarcoma											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	362	461	448	449	499	560	589	616	631	633	636	638	643	647	647	652	652	653	653	673	673	675	675	689	692
Carcass ID Number	020	004	003	015	056	060	061	028	021	010	032	025	042	040	059	014	048	050	051	090	057	024	052	044	019
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																									
Skeletal muscle			+					+																	
Sarcoma, metastatic, mesentery								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X						X								
Alveolar/bronchiolar adenoma, multiple, two																									
Alveolar/bronchiolar carcinoma					X																	X			
Cholangiocarcinoma, metastatic, liver																					X				
Hepatocellular carcinoma, metastatic, liver										X															
Histiocytic sarcoma																									
Sarcoma, metastatic, mesentery								X																	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung					X																				
Mediastinum, hemangiosarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye															+										
Harderian gland		+													+	+				+					+
Adenoma		X													X					X					X
Carcinoma																X									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung					X																				
Cholangiocarcinoma, metastatic, liver																					X				
Histiocytic sarcoma																									
Renal tubule, adenoma																									
Urethra												+													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Histiocytic sarcoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant mixed			X						X										X					X	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	702	707	707	707	707	708	709	727	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	054	012	018	037	060	053	049	041	011	007	008	011	013	017	026	027	029	030	031	033	034	035	036	038	039
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																										
Skeletal muscle																										
Sarcoma, metastatic, mesentery																										
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X		X	X			X						X								X				
Alveolar/bronchiolar adenoma, multiple, two			X																		X					
Alveolar/bronchiolar carcinoma																			X							
Cholangiocarcinoma, metastatic, liver																										
Hepatocellular carcinoma, metastatic, liver		X				X																		X		
Histiocytic sarcoma																		X								
Sarcoma, metastatic, mesentery																										
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										
Mediastinum, hemangiosarcoma																						X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye			+																							
Harderian gland			+											+												+
Adenoma			X											X												
Carcinoma																										X
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																										
Cholangiocarcinoma, metastatic, liver																										
Histiocytic sarcoma							X																			
Renal tubule, adenoma												X														
Urethra																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																			
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X											X								
Lymphoma malignant mixed			X												X											X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	
Carcass ID Number	055	058	002	005	022	023	043	045	046	047	Total Tissues/ Tumors
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Osteoma				X							1
Skeletal muscle											2
Sarcoma, metastatic, mesentery											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma						X		X			10
Alveolar/bronchiolar adenoma, multiple, two											2
Alveolar/bronchiolar carcinoma								X			4
Cholangiocarcinoma, metastatic, liver											1
Hepatocellular carcinoma, metastatic, liver											4
Histiocytic sarcoma											1
Sarcoma, metastatic, mesentery											1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung											1
Mediastinum, hemangiosarcoma											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Eye											2
Harderian gland		+						+			10
Adenoma		X						X			8
Carcinoma											2
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar carcinoma, metastatic, lung											1
Cholangiocarcinoma, metastatic, liver											1
Histiocytic sarcoma											1
Renal tubule, adenoma											1
Urethra											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Histiocytic sarcoma											1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Lymphoma malignant mixed											7

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL

Number of Days on Study	049	073	210	312	469	531	531	597	615	621	630	640	645	647	702	705	706	707	709	710	724	727	727	727	729
Carcass ID Number	088	091	113	198	066	069	081	107	068	015	155	100	141	111	108	087	062	161	096	094	047	065	073	073	061
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+
Hemangioma																		X							
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+
Polyp adenomatous																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma					X																				
Hemangioma																									
Hemangiosarcoma										X															
Hepatoblastoma																	X		X						
Hepatocellular carcinoma						X		X			X	X						X					X		
Hepatocellular carcinoma, multiple					X					X						X								X	X
Hepatocellular adenoma				X		X				X				X					X		X	X			
Hepatocellular adenoma, multiple									X			X	X		X		X			X				X	
Mesentery										+													+	+	
Hemangiosarcoma										X															
Hepatocellular carcinoma, metastatic, liver																								X	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Squamous cell papilloma																		X							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Tooth									+	+	+	+	+		+	+			+	+	+	+	+		+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pericardium, cholangiocarcinoma, metastatic, liver					X																				
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																	X			X	X				X
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Carcinoma														X											
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I
Pars distalis, adenoma																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	063	064	067	070	071	072	074	075	076	078	079	080	082	083	084	085	086	089	090	092	093	095	097	099	101
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous				X																					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Hemangioma															X						X				
Hemangiosarcoma											X					X	X								X
Hepatoblastoma																									
Hepatocellular carcinoma									X	X						X		X		X	X		X		
Hepatocellular carcinoma, multiple				X		X							X		X		X		X			X			
Hepatocellular adenoma															X				X	X					
Hepatocellular adenoma, multiple		X	X		X	X	X	X	X		X		X	X		X	X	X			X		X	X	
Mesentery	+					+																			
Hemangiosarcoma																									
Hepatocellular carcinoma, metastatic, liver																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+		+	+			+	+		+	+	+		+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel															+										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pericardium, cholangiocarcinoma, metastatic, liver																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																		X							
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																		X							
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	102	104	106	109	110	112	117	118	119	120	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	+	+	+	+	57
Intestine large, colon	+	+	+	+	+	+	M	+	+	+	56
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	57
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	56
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	56
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	56
Hemangioma											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	56
Polyp adenomatous											1
Liver	+	+	+	+	+	+	+	+	+	+	60
Cholangiocarcinoma											1
Hemangioma											2
Hemangiosarcoma											5
Hepatoblastoma											2
Hepatocellular carcinoma	X										14
Hepatocellular carcinoma, multiple		X			X			X			15
Hepatocellular adenoma		X	X			X	X	X			15
Hepatocellular adenoma, multiple	X								X	X	26
Mesentery										+	6
Hemangiosarcoma											1
Hepatocellular carcinoma, metastatic, liver											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	59
Squamous cell papilloma											2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Tooth	+	+	+	+		+	+		+	+	41
Cardiovascular System											
Blood vessel											1
Heart	+	+	+	+	+	+	+	+	+	+	60
Pericardium, cholangiocarcinoma, metastatic, liver											1
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Subcapsular, adenoma											5
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Carcinoma											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	59
Pituitary gland	+	+	+	+	+	+	+	+	+	+	57
Pars distalis, adenoma											1
Pars intermedia, adenoma					X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	59

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	0	0	2	3	4	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	4	7	1	1	6	3	3	9	1	2	3	4	4	4	0	0	0	0	0	1	2	2	2	2	2
	9	3	0	2	9	1	1	7	5	1	0	0	5	7	2	5	6	7	9	0	4	7	7	7	9
Carcass ID Number	0	0	1	0	0	0	0	1	0	1	1	1	1	1	1	0	0	1	0	0	0	0	0	1	0
	8	9	1	9	6	6	8	0	6	0	1	0	1	1	0	8	6	1	9	9	7	6	7	0	6
	8	1	3	8	6	9	1	7	8	5	5	0	4	1	8	7	2	6	6	4	7	5	3	3	1
General Body System																									
Tissue NOS			+																						
Thoracic, sarcoma			X																						
Genital System																									
Coagulating gland															+		+		+	+	+		+		+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis							+																		
Preputial gland								+	+	+	+	+				+		+	+		+		+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood			+																						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node					+		+																		
Mediastinal, cholangiocarcinoma, metastatic, liver					X																				
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Hemangiosarcoma										X															
Histiocytic sarcoma																									
Thymus	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	I	+	+
Integumentary System																									
Mammary gland	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma									X																
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, hemangiosarcoma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma														X											
Hepatocellular carcinoma, metastatic, liver										X														X	
Pleura, cholangiocarcinoma, metastatic, liver					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	063	064	067	070	071	072	074	075	076	078	079	080	082	083	084	085	086	089	090	092	093	095	097	099	101
General Body System																									
Tissue NOS																									
Thoracic, sarcoma																									
Genital System																									
Coagulating gland								+								+			+				+		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+	+	+	+	+	+			+		+	+	+		+	+			+		+	+		+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Lymph node																+			+						
Mediastinal, cholangiocarcinoma, metastatic, liver																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Histiocytic sarcoma								X																	
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangioma					X																				
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X	X												X
Alveolar/bronchiolar carcinoma																			X						
Hepatocellular carcinoma, metastatic, liver																X									
Pleura, cholangiocarcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	102	104	106	109	110	112	117	118	119	120	Total Tissues/ Tumors
General Body System											
Tissue NOS											1
Thoracic, sarcoma											1
Genital System											
Coagulating gland				+		+					13
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Penis											1
Preputial gland	+	+		+	+	+	+	+		+	36
Prostate	+	+	+	+	+	+	+	+	+	+	60
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	60
Testes	+	+	+	+	+	+	+	+	+	+	60
Hematopoietic System											
Blood											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Lymph node						+					5
Mediastinal, cholangiocarcinoma, metastatic, liver											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	59
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	58
Histiocytic sarcoma											1
Spleen	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma											2
Histiocytic sarcoma											1
Thymus	+	+	+	+	+	+	+	+	+	+	54
Integumentary System											
Mammary gland	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	60
Subcutaneous tissue, fibrosarcoma											1
Subcutaneous tissue, hemangioma						X					2
Subcutaneous tissue, hemangiosarcoma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma				X						X	6
Alveolar/bronchiolar carcinoma											2
Hepatocellular carcinoma, metastatic, liver											3
Pleura, cholangiocarcinoma, metastatic, liver											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	049	073	210	312	469	531	531	597	615	621	630	640	645	647	702	705	706	707	709	710	724	727	727	727	729
Carcass ID Number	088	091	113	098	066	069	081	097	068	065	015	010	014	011	108	087	062	061	096	094	077	065	073	073	061
Special Senses System																										
Harderian gland															+											
Adenoma															X											
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	
Renal tubule, adenocarcinoma																										
Renal tubule, adenoma																										
Urethra													+													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	
Hemangioma																X										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma																										
Lymphoma malignant mixed															X											

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	063	064	067	070	071	072	074	075	076	078	079	080	082	083	084	085	086	089	090	092	093	095	097	099	101
Special Senses System																										
Harderian gland									+																	
Adenoma									X																	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenocarcinoma																							X			
Renal tubule, adenoma																										
Urethra																		+								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																		
Lymphoma malignant mixed																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	102	104	106	109	110	112	117	118	119	120	Total Tissues/ Tumors
Special Senses System											
Harderian gland						+					3
Adenoma						X					3
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	58
Renal tubule, adenocarcinoma											1
Renal tubule, adenoma	X										1
Urethra											2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Hemangioma											1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Lymphoma malignant mixed				X							2

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL

Number of Days on Study	076	043	048	052	056	058	058	058	061	061	061	062	064	064	064	064	067	067	069	070	070	070	072	072	072
Carcass ID Number	130	165	146	143	164	125	168	163	153	177	157	155	173	174	132	156	129	154	166	131	144	147	171	124	139
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									X
Polyp adenomatous																						X			
Intestine small, ileum	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																	X					
Hepatoblastoma																								X	
Hepatocellular carcinoma		X		X				X	X		X		X		X	X	X		X			X			
Hepatocellular carcinoma, multiple					X									X									X		X
Hepatocellular adenoma				X	X						X	X	X		X				X	X	X	X			X
Hepatocellular adenoma, multiple						X										X	X	X						X	
Histiocytic sarcoma						X																			
Mesentery			+			+															+				+
Histiocytic sarcoma						X																			
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth			+				+						+			+	+	+	+	+	+		+		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma											X											X			
General Body System																									
None																									
Genital System																									
Coagulating gland																+		+	+						
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Preputial gland											+					+		+		+		+	+	+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728
Carcass ID Number	142	121	122	123	126	127	128	133	134	135	136	137	138	140	141	145	148	149	150	151	152	158	159	160	161
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma														X											
Polyp adenomatous																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatoblastoma								X					X		X										
Hepatocellular carcinoma		X		X	X			X		X						X			X	X					
Hepatocellular carcinoma, multiple											X	X	X		X		X	X						X	
Hepatocellular adenoma		X						X			X		X					X	X		X				X
Hepatocellular adenoma, multiple	X		X	X	X		X		X					X	X					X		X	X		
Histiocytic sarcoma																									
Mesentery								+																	
Histiocytic sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+		+		+	+	+	+		+		+	+	+		+	+		+	+	+	+		+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X												X								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma						X																			
General Body System																									
None																									
Genital System																									
Coagulating gland	+	+		+			+						+	+	+	+	+		+			+	+	+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Preputial gland	+			+	+			+	+	+	+	+	+		+				+	+				+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	162	167	169	170	172	175	176	178	179	180	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	+	+	+	+	59
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	58
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	58
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	58
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	57
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	57
Adenocarcinoma											2
Polyp adenomatous											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	57
Liver	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma											2
Hepatoblastoma											4
Hepatocellular carcinoma							X	X			21
Hepatocellular carcinoma, multiple					X				X	X	14
Hepatocellular adenoma	X				X			X			22
Hepatocellular adenoma, multiple			X	X		X	X		X	X	22
Histiocytic sarcoma											1
Mesentery	+						+				7
Histiocytic sarcoma											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	59
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Tooth	+		+	+	+	+		+			33
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adenoma											2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	56
Pituitary gland	+	+	+	+	+	M	+	+	+	+	56
Thyroid gland	+	+	+	+	+	+	+	+	+	+	59
Follicular cell, adenoma									X		4
General Body System											
None											
Genital System											
Coagulating gland						+		+	+	+	21
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Preputial gland	+		+	+						+	24
Prostate	+	+	+	+	+	+	+	+	+	+	60
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	60
Testes	+	+	+	+	+	+	+	+	+	+	60

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	0	4	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7		
	7	3	8	2	6	8	8	8	1	1	1	2	4	4	4	4	7	7	9	0	0	0	2	2		
	6	4	6	6	2	0	0	9	1	2	6	2	6	6	7	7	4	5	5	7	7	9	1	7		
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	3	6	4	4	6	2	6	6	5	7	5	5	7	7	3	5	2	5	6	3	4	4	7	2		
	0	5	6	3	4	5	8	3	3	7	7	5	3	4	2	6	9	4	6	1	4	7	1	4		9
Hematopoietic System																										
Blood																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																										
Lymph node, mandibular	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Thymus	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymocyte, thymoma malignant																										
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																							+			
Spinal cord																							+			
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X									X	X		
Alveolar/bronchiolar carcinoma																		X				X				
Hepatocellular carcinoma, metastatic, liver					X						X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear																	+									
Pinna, fibrosarcoma																										
Eye																								+		
Harderian gland																								+		
Adenoma																								X		
Carcinoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																				
Lymphoma malignant mixed												X									X					X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728
Carcass ID Number	142	121	122	123	126	127	128	133	134	135	136	137	138	140	141	145	148	149	150	151	152	158	159	160	161
Hematopoietic System																										
Blood									+																	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																	+								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Thymus	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Thymocyte, thymoma malignant																				X					
Integumentary System																									
Mammary gland	M	M	M	+	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X							X															
Alveolar/bronchiolar carcinoma													X												
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Pinna, fibrosarcoma																									
Eye																									
Harderian gland															+			+							
Adenoma																		X							
Carcinoma															X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma		X																							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Lymphoma malignant mixed		X																X							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	162	167	169	170	172	175	176	178	179	180	Total Tissues/ Tumors
Hematopoietic System											
Blood											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	58
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	57
Spleen	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma											1
Thymus	+	+	+	+	+	+	+	+	+	+	55
Thymocyte, thymoma malignant											1
Integumentary System											
Mammary gland	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	60
Basal cell adenoma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Peripheral nerve											1
Spinal cord											1
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma								X			6
Alveolar/bronchiolar carcinoma											3
Hepatocellular carcinoma, metastatic, liver											2
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Ear										+	2
Pinna, fibrosarcoma										X	1
Eye											1
Harderian gland											3
Adenoma											2
Carcinoma											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	59
Urinary bladder	+	+	+	+	+	+	+	+	+	+	58
Hemangioma											1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Lymphoma malignant mixed											5

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL

Number of Days on Study	093	094	106	112	118	125	139	146	174	189	269	318	360	370	386	396	460	468	486	489	511	529	531	552	567
Carcass ID Number	222	236	212	190	198	191	223	215	226	227	203	237	230	205	206	286	282	289	220	294	192	228	234	183	184
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	A	+	+	+	A	M	M	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Polyp adenomatous																					X				
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma																									
Hepatoblastoma, multiple																									
Hepatocellular carcinoma																					X		X		
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																X		X		X	X				
Hepatocellular adenoma, multiple																									
Mesentery												+													
Pancreas	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Tooth													+							+					+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	M	M	M	I	+	+	+	+	+	M	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland																	+	+						+	
Prostate	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	577	580	602	611	614	625	628	630	671	684	684	687	700	708	709	709	726	727	728	728	728	728	728	728	728
Carcass ID Number	232	214	187	208	197	207	193	238	196	188	225	210	213	204	189	229	195	216	181	185	200	201	202	209	211
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma												X			X										
Hepatoblastoma, multiple								X																	
Hepatocellular carcinoma	X			X	X		X			X			X	X		X	X		X				X		
Hepatocellular carcinoma, multiple			X									X			X						X	X			
Hepatocellular adenoma	X	X						X		X	X						X							X	
Hepatocellular adenoma, multiple						X								X		X			X			X	X		X
Mesentery			+													+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+						+	+	+		+	+		+	+	+	+			+	+	+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma							X																		
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
Follicular cell, carcinoma		X																							
General Body System																									
None																									
Genital System																									
Coagulating gland	+					+														+		+			
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+				+	+			+			+		+						+		+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	213	217	218	219	221	224	233	235	239	240	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	+	+	+	+	54
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	56
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	57
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	55
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	56
Polyp adenomatous											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	55
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	55
Liver	+	+	+	+	+	+	+	+	+	+	59
Hepatoblastoma											2
Hepatoblastoma, multiple											1
Hepatocellular carcinoma				X							14
Hepatocellular carcinoma, multiple											5
Hepatocellular adenoma	X				X						13
Hepatocellular adenoma, multiple		X	X			X	X		X	X	13
Mesentery		+									4
Pancreas	+	+	+	+	+	+	+	+	+	+	57
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	58
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	57
Tooth	+	+	+	+		+	+	+	+		26
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Subcapsular, adenoma									X		2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	57
Parathyroid gland	+	M	+	+	+	+	+	M	M	+	55
Pituitary gland	+	+	+	+	+	+	+	+	+	+	53
Thyroid gland	+	+	+	+	+	+	+	+	+	+	57
Follicular cell, adenoma							X				1
Follicular cell, carcinoma											1
General Body System											
None											
Genital System											
Coagulating gland											4
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Preputial gland		+	+	+	+	+	+	+	+		21
Prostate	+	+	+	+	+	+	+	+	+	+	58
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	60
Testes	+	+	+	+	+	+	+	+	+	+	59

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	0	0	1	1	1	1	1	1	1	1	2	3	3	3	3	3	4	4	4	4	5	5	5	5	5
	9	9	0	1	1	2	3	4	7	8	6	1	6	7	8	9	6	8	8	8	1	2	3	5	6
	3	4	6	2	8	5	9	6	4	9	9	8	0	0	6	6	0	6	6	9	1	9	1	2	7
Carcass ID Number	2	2	2	1	1	1	2	2	2	2	2	2	2	2	2	1	1	1	2	1	1	2	2	1	1
	2	3	1	9	9	9	2	1	2	2	0	3	3	0	0	8	8	9	2	9	9	2	3	8	8
	2	6	2	0	8	1	3	5	6	7	3	7	0	5	6	6	2	9	0	4	2	8	4	3	4
Hematopoietic System																									
Blood									+																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node												+													
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+		+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	M	M	A	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Hemangiosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X				X												
Alveolar/bronchiolar carcinoma																						X			
Carcinoma												X													
Hepatoblastoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																		+							
Adenoma																		X							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Renal tubule, adenocarcinoma																									
Ureter												+													
Urethra												+													
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	577	580	602	611	614	625	628	630	671	684	684	687	700	708	709	709	726	727	728	728	728	728	728	728	728
Carcass ID Number	232	214	187	208	197	207	193	238	196	188	225	210	213	204	189	229	195	216	181	185	200	201	202	209	201
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Lymph node																									
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma													X												
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	I	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																					+				
Hemangiosarcoma																					X				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X		X			
Alveolar/bronchiolar carcinoma													X												
Carcinoma																									
Hepatoblastoma, metastatic, liver								X																	
Hepatocellular carcinoma, metastatic, liver			X	X									X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenocarcinoma																		X							
Ureter																									
Urethra		+							+																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed						X			X																

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	213	117	118	119	121	124	233	235	239	240	Total Tissues/ Tumors
Hematopoietic System											
Blood											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Lymph node											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	56
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	56
Spleen	+	+	+	+	+	+	+	+	+	+	57
Hemangioma											1
Hemangiosarcoma			X								1
Thymus	+	+	+	+	+	+	+	+	+	+	52
Integumentary System											
Mammary gland	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	60
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											1
Hemangiosarcoma											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											4
Alveolar/bronchiolar carcinoma											2
Carcinoma											1
Hepatoblastoma, metastatic, liver											1
Hepatocellular carcinoma, metastatic, liver											3
Nose	+	+	+	+	+	+	+	+	+	+	59
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Harderian gland											1
Adenoma											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	57
Renal tubule, adenocarcinoma											1
Ureter											1
Urethra											3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed											2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Adrenal Cortex: Adenoma				
Overall rate[a]	4/60 (7%)	5/60 (8%)	2/60 (3%)	2/60 (3%)
Adjusted rate[b]	13.7%	12.2%	5.9%	9.1%
Terminal rate[c]	3/27 (11%)	2/36 (6%)	2/34 (6%)	1/17 (6%)
First incidence (days)	707	706	728 (T)	628
Life table test[d]	P=0.356N	P=0.592N	P=0.240N	P=0.566N
Logistic regression test[d]	P=0.344N	P=0.619	P=0.248N	P=0.545N
Cochran-Armitage test[d]	P=0.180N			
Fisher exact test[d]		P=0.500	P=0.340N	P=0.340N
Harderian Gland: Adenoma				
Overall rate	8/60 (13%)	3/60 (5%)	2/60 (3%)	1/60 (2%)
Adjusted rate	21.3%	7.6%	5.6%	2.3%
Terminal rate	3/27 (11%)	2/36 (6%)	1/34 (3%)	0/17 (0%)
First incidence (days)	461	702	727	486
Life table test	P=0.027N	P=0.057N	P=0.032N	P=0.079N
Logistic regression test	P=0.015N	P=0.104N	P=0.049N	P=0.030N
Cochran-Armitage test	P=0.010N			
Fisher exact test		P=0.102N	P=0.047N	P=0.016N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	10/60 (17%)	3/60 (5%)	3/60 (5%)	1/60 (2%)
Adjusted rate	26.2%	7.6%	8.4%	2.3%
Terminal rate	4/27 (15%)	2/36 (6%)	2/34 (6%)	0/17 (0%)
First incidence (days)	461	702	727	486
Life table test	P=0.013N	P=0.019N	P=0.023N	P=0.039N
Logistic regression test	P=0.007N	P=0.039N	P=0.038N	P=0.012N
Cochran-Armitage test	P=0.004N			
Fisher exact test		P=0.037N	P=0.037N	P=0.004N
Liver: Hemangiosarcoma				
Overall rate	3/59 (5%)	5/60 (8%)	2/59 (3%)	0/59 (0%)
Adjusted rate	9.3%	12.9%	4.1%	0.0%
Terminal rate	2/27 (7%)	4/36 (11%)	0/34 (0%)	0/17 (0%)
First incidence (days)	636	621	486	–[e]
Life table test	P=0.104N	P=0.476	P=0.446N	P=0.227N
Logistic regression test	P=0.072N	P=0.383	P=0.499N	P=0.193N
Cochran-Armitage test	P=0.051N			
Fisher exact test		P=0.368	P=0.500N	P=0.122N
Liver: Hepatocellular Adenoma				
Overall rate	40/59 (68%)	41/60 (68%)	44/59 (75%)	26/59 (44%)
Adjusted rate	90.3%	81.7%	86.1%	85.1%
Terminal rate	23/27 (85%)	27/36 (75%)	27/34 (79%)	13/17 (76%)
First incidence (days)	498	312	526	396
Life table test	P=0.389	P=0.132N	P=0.368N	P=0.527
Logistic regression test	P=0.276N	P=0.542	P=0.330	P=0.326N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.553	P=0.271	P=0.008N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Liver: Hepatocellular Carcinoma				
Overall rate	25/59 (42%)	29/60 (48%)	35/59 (59%)	19/59 (32%)
Adjusted rate	59.4%	61.9%	70.3%	58.8%
Terminal rate	12/27 (44%)	19/36 (53%)	20/34 (59%)	5/17 (29%)
First incidence (days)	461	469	434	511
Life table test	P=0.190	P=0.464N	P=0.253	P=0.332
Logistic regression test	P=0.530	P=0.306	P=0.050	P=0.565
Cochran-Armitage test	P=0.132N			
Fisher exact test		P=0.320	P=0.049	P=0.171N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	47/59 (80%)	52/60 (87%)	54/59 (92%)	36/59 (61%)
Adjusted rate	95.8%	92.9%	96.4%	94.4%
Terminal rate	25/27 (93%)	32/36 (89%)	32/34 (94%)	15/17 (88%)
First incidence (days)	461	312	434	396
Life table test	P=0.097	P=0.238N	P=0.476N	P=0.171
Logistic regression test	P=0.504	P=0.117	P=0.053	P=0.401
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.219	P=0.057	P=0.022N
Liver: Hepatoblastoma				
Overall rate	2/59 (3%)	2/60 (3%)	4/59 (7%)	3/59 (5%)
Adjusted rate	4.9%	4.6%	11.3%	12.0%
Terminal rate	0/27 (0%)	0/36 (0%)	3/34 (9%)	0/17 (0%)
First incidence (days)	647	706	727	630
Life table test	P=0.155	P=0.610N	P=0.426	P=0.298
Logistic regression test	P=0.198	P=0.688N	P=0.371	P=0.369
Cochran-Armitage test	P=0.355			
Fisher exact test		P=0.684N	P=0.340	P=0.500
Liver: Hepatoblastoma or Hepatocellular Carcinoma				
Overall rate	27/59 (46%)	31/60 (52%)	36/59 (61%)	20/59 (34%)
Adjusted rate	61.4%	63.7%	71.1%	60.3%
Terminal rate	12/27 (44%)	19/36 (53%)	20/34 (59%)	5/17 (29%)
First incidence (days)	461	469	434	511
Life table test	P=0.223	P=0.439N	P=0.321	P=0.351
Logistic regression test	P=0.484N	P=0.307	P=0.072	P=0.544N
Cochran-Armitage test	P=0.091N			
Fisher exact test		P=0.323	P=0.070	P=0.130N
Liver: Hepatoblastoma, Hepatocellular Adenoma, or Carcinoma				
Overall rate	48/59 (81%)	52/60 (87%)	54/59 (92%)	36/59 (61%)
Adjusted rate	95.9%	92.9%	96.4%	94.4%
Terminal rate	25/27 (93%)	32/36 (89%)	32/34 (94%)	15/17 (88%)
First incidence (days)	461	312	434	396
Life table test	P=0.120	P=0.192N	P=0.414N	P=0.206
Logistic regression test	P=0.521N	P=0.169	P=0.084	P=0.484
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.295	P=0.089	P=0.012N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	12/60 (20%)	6/60 (10%)	6/60 (10%)	4/60 (7%)
Adjusted rate	33.6%	16.7%	15.4%	15.3%
Terminal rate	5/27 (19%)	6/36 (17%)	3/34 (9%)	2/17 (12%)
First incidence (days)	636	728 (T)	646	174
Life table test	P=0.124N	P=0.035N	P=0.051N	P=0.163N
Logistic regression test	P=0.067N	P=0.059N	P=0.075N	P=0.066N
Cochran-Armitage test	P=0.028N			
Fisher exact test		P=0.100N	P=0.100N	P=0.029N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/60 (7%)	2/60 (3%)	3/60 (5%)	3/60 (5%)
Adjusted rate	11.4%	4.8%	7.6%	8.7%
Terminal rate	2/27 (7%)	1/36 (3%)	1/34 (3%)	0/17 (0%)
First incidence (days)	498	647	675	318
Life table test	P=0.455	P=0.267N	P=0.409N	P=0.609
Logistic regression test	P=0.499N	P=0.336N	P=0.500N	P=0.476N
Cochran-Armitage test	P=0.500N			
Fisher exact test		P=0.340N	P=0.500N	P=0.500N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	15/60 (25%)	8/60 (13%)	9/60 (15%)	7/60 (12%)
Adjusted rate	39.3%	21.2%	22.1%	22.6%
Terminal rate	6/27 (22%)	7/36 (19%)	4/34 (12%)	2/17 (12%)
First incidence (days)	498	647	646	174
Life table test	P=0.279N	P=0.028N	P=0.063N	P=0.276N
Logistic regression test	P=0.108N	P=0.071N	P=0.110N	P=0.074N
Cochran-Armitage test	P=0.058N			
Fisher exact test		P=0.082N	P=0.127N	P=0.049N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/60 (2%)	0/59 (0%)	4/59 (7%)	1/57 (2%)
Adjusted rate	3.6%	0.0%	10.1%	5.9%
Terminal rate	0/27 (0%)	0/36 (0%)	2/34 (6%)	1/17 (6%)
First incidence (days)	727	–	616	728 (T)
Life table test	P=0.269	P=0.434N	P=0.247	P=0.656
Logistic regression test	P=0.300	P=0.439N	P=0.186	P=0.672
Cochran-Armitage test	P=0.426			
Fisher exact test		P=0.504N	P=0.177	P=0.739
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/60 (2%)	0/59 (0%)	4/59 (7%)	2/57 (4%)
Adjusted rate	3.6%	0.0%	10.1%	8.7%
Terminal rate	0/27 (0%)	0/36 (0%)	2/34 (6%)	1/17 (6%)
First incidence (days)	727	–	616	580
Life table test	P=0.099	P=0.434N	P=0.247	P=0.345
Logistic regression test	P=0.144	P=0.439N	P=0.186	P=0.386
Cochran-Armitage test	P=0.222			
Fisher exact test		P=0.504N	P=0.177	P=0.481

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
All Organs: Hemangioma				
Overall rate	0/60 (0%)	6/60 (10%)	1/60 (2%)	1/60 (2%)
Adjusted rate	0.0%	15.1%	2.9%	4.3%
Terminal rate	0/27 (0%)	4/36 (11%)	1/34 (3%)	0/17 (0%)
First incidence (days)	–	705	728 (T)	707
Life table test	P=0.593N	P=0.040	P=0.546	P=0.422
Logistic regression test	P=0.589N	P=0.028	P=0.546	P=0.415
Cochran-Armitage test	P=0.404N			
Fisher exact test		P=0.014	P=0.500	P=0.500
All Organs: Hemangiosarcoma				
Overall rate	4/60 (7%)	7/60 (12%)	3/60 (5%)	2/60 (3%)
Adjusted rate	12.9%	17.7%	6.9%	11.8%
Terminal rate	3/27 (11%)	5/36 (14%)	1/34 (3%)	2/17 (12%)
First incidence (days)	636	621	486	728 (T)
Life table test	P=0.331N	P=0.411	P=0.419N	P=0.576N
Logistic regression test	P=0.279N	P=0.300	P=0.500N	P=0.549N
Cochran-Armitage test	P=0.147N			
Fisher exact test		P=0.264	P=0.500N	P=0.340N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/60 (7%)	13/60 (22%)	4/60 (7%)	3/60 (5%)
Adjusted rate	12.9%	31.6%	9.8%	15.6%
Terminal rate	3/27 (11%)	9/36 (25%)	2/34 (6%)	2/17 (12%)
First incidence (days)	636	621	486	707
Life table test	P=0.349N	P=0.062	P=0.551N	P=0.559
Logistic regression test	P=0.308N	P=0.027	P=0.641N	P=0.582
Cochran-Armitage test	P=0.122N			
Fisher exact test		P=0.017	P=0.641N	P=0.500N
All Organs: Malignant Lymphoma (Mixed)				
Overall rate	7/60 (12%)	2/60 (3%)	5/60 (8%)	2/60 (3%)
Adjusted rate	17.7%	4.9%	12.5%	6.9%
Terminal rate	2/27 (7%)	1/36 (3%)	2/34 (6%)	0/17 (0%)
First incidence (days)	486	702	622	625
Life table test	P=0.270N	P=0.054N	P=0.300N	P=0.251N
Logistic regression test	P=0.171N	P=0.083N	P=0.380N	P=0.138N
Cochran-Armitage test	P=0.110N			
Fisher exact test		P=0.081N	P=0.381N	P=0.081N
All Organs: Benign Neoplasms				
Overall rate	47/60 (78%)	49/60 (82%)	50/60 (83%)	31/60 (52%)
Adjusted rate	93.7%	94.2%	94.3%	90.1%
Terminal rate	24/27 (89%)	33/36 (92%)	31/34 (91%)	14/17 (82%)
First incidence (days)	461	312	526	174
Life table test	P=0.380	P=0.122N	P=0.272N	P=0.494
Logistic regression test	P=0.164N	P=0.319	P=0.353	P=0.188N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.410	P=0.322	P=0.002N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
All Organs: Malignant Neoplasms				
Overall rate	41/60 (68%)	40/60 (67%)	43/60 (72%)	27/60 (45%)
Adjusted rate	80.9%	75.0%	76.4%	70.3%
Terminal rate	18/27 (67%)	23/36 (64%)	21/34 (62%)	6/17 (35%)
First incidence (days)	461	210	434	318
Life table test	P=0.390	P=0.135N	P=0.343N	P=0.504
Logistic regression test	P=0.106N	P=0.533N	P=0.423	P=0.197N
Cochran-Armitage test	P=0.004N			
Fisher exact test		P=0.500N	P=0.421	P=0.008N
All Organs: Benign or Malignant Neoplasms				
Overall rate	56/60 (93%)	56/60 (93%)	56/60 (93%)	43/60 (72%)
Adjusted rate	100.0%	98.2%	98.2%	97.7%
Terminal rate	27/27 (100%)	35/36 (97%)	33/34 (97%)	16/17 (94%)
First incidence (days)	461	210	434	174
Life table test	P=0.084	P=0.061N	P=0.134N	P=0.156
Logistic regression test	P=0.280N	P=0.315	P=0.661	P=0.615N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.641N	P=0.641N	P=0.002N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Chlorinated and Chloraminated Water	30/50	12/50	35/50
t-Butyl Alcohol	40/59	25/59	47/59
Overall Historical Incidence			
Total	144/239 (60.3%)	67/239 (28.0%)	171/239 (71.6%)
Standard deviation	9.0%	13.5%	12.3%
Range	47%-68%	10%-42%	53%-80%

[a] Data as of 31 March 1993

TABLE C4b
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Chlorinated and Chloraminated Water	1/50	0/50	1/50
t-Butyl Alcohol	1/60	0/60	1/60
Overall Historical Incidence			
Total	4/240 (1.7%)	0/240 (0.0%)	4/240 (1.7%)
Standard deviation	0.5%		0.5%
Range	1%-2%		1%-2%

[a] Data as of 31 March 1993

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Disposition Summary				
Animals initially in study	60	60	60	60
Early deaths				
Accidental deaths		2	1	
Moribund	20	14	19	21
Natural deaths	13	8	6	22
Survivors				
Terminal sacrifice	27	36	34	17
Animals examined microscopically	60	60	60	60
Alimentary System				
Esophagus	(60)	(60)	(60)	(60)
Inflammation, focal, suppurative				1 (2%)
Gallbladder	(55)	(57)	(59)	(54)
Cyst	1 (2%)			
Intestine small, duodenum	(56)	(56)	(57)	(56)
Ulcer		1 (2%)		
Intestine small, jejunum	(56)	(56)	(57)	(55)
Hyperplasia, lymphoid			1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)			1 (2%)
Ulcer				1 (2%)
Intestine small, ileum	(56)	(56)	(57)	(55)
Hyperplasia, lymphoid	2 (4%)			
Liver	(59)	(60)	(59)	(59)
Angiectasis		3 (5%)	1 (2%)	
Basophilic focus	2 (3%)	8 (13%)	10 (17%)	6 (10%)
Clear cell focus	10 (17%)	25 (42%)	21 (36%)	20 (34%)
Congestion			1 (2%)	
Eosinophilic focus	20 (34%)	24 (40%)	31 (53%)	10 (17%)
Fatty change	12 (20%)	5 (8%)	8 (14%)	29 (49%)
Fibrosis, focal		1 (2%)		
Focal cellular change				2 (3%)
Hematopoietic cell proliferation	2 (3%)	1 (2%)		
Hemorrhage		1 (2%)	1 (2%)	
Infarct	2 (3%)	1 (2%)	2 (3%)	
Infiltration cellular, mixed cell			1 (2%)	
Inflammation, focal	2 (3%)		3 (5%)	
Mixed cell focus	4 (7%)	4 (7%)	3 (5%)	5 (8%)
Necrosis, focal	5 (8%)	3 (5%)	5 (8%)	1 (2%)
Tension lipidosis				5 (8%)
Thrombosis			1 (2%)	
Centrilobular, necrosis		1 (2%)	1 (2%)	1 (2%)
Mesentery	(5)	(6)	(7)	(4)
Angiectasis				1 (25%)
Cyst			1 (14%)	
Hemorrhage	1 (20%)			
Hyperplasia, mast cell		1 (17%)		
Inflammation, chronic	1 (20%)		2 (29%)	1 (25%)
Mineralization	1 (20%)			
Fat, necrosis	1 (20%)	3 (50%)	3 (43%)	2 (50%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Alimentary System (continued)				
Pancreas	(58)	(59)	(59)	(57)
Atrophy, focal	3 (5%)	2 (3%)	1 (2%)	
Edema	1 (2%)		1 (2%)	
Necrosis				1 (2%)
Duct, dilatation		1 (2%)		
Stomach, forestomach	(59)	(59)	(59)	(58)
Erosion		2 (3%)		
Inflammation, chronic	6 (10%)	4 (7%)	1 (2%)	7 (12%)
Ulcer	1 (2%)	1 (2%)	1 (2%)	4 (7%)
Mucosa, hyperplasia	7 (12%)	7 (12%)	1 (2%)	4 (7%)
Stomach, glandular	(59)	(59)	(59)	(57)
Erosion		1 (2%)		3 (5%)
Inflammation, chronic	1 (2%)			
Mineralization	1 (2%)			2 (4%)
Pigmentation	1 (2%)	3 (5%)		2 (4%)
Mucosa, hyperplasia	4 (7%)			2 (4%)
Tooth	(44)	(41)	(33)	(26)
Incisor, dysplasia	44 (100%)	41 (100%)	33 (100%)	26 (100%)
Incisor, inflammation, suppurative			1 (3%)	
Cardiovascular System				
Blood vessel	(1)	(1)		
Mesenteric artery, inflammation, chronic	1 (100%)			
Endocrine System				
Adrenal cortex	(60)	(60)	(60)	(60)
Accessory adrenal cortical nodule		1 (2%)		2 (3%)
Cyst	1 (2%)	1 (2%)	1 (2%)	
Focal cellular change	2 (3%)	6 (10%)	1 (2%)	1 (2%)
Subcapsular, hyperplasia, focal	5 (8%)	7 (12%)	7 (12%)	1 (2%)
Parathyroid gland	(55)	(59)	(56)	(55)
Cyst	2 (4%)			2 (4%)
Degeneration, cystic		1 (2%)		
Pituitary gland	(52)	(57)	(56)	(53)
Cyst	2 (4%)	1 (2%)		3 (6%)
Pars distalis, focal cellular change	1 (2%)			
Thyroid gland	(60)	(59)	(59)	(57)
Cyst	1 (2%)			
Degeneration, cystic	7 (12%)	5 (8%)	10 (17%)	5 (9%)
Inflammation, focal			1 (2%)	
Follicle, cyst	1 (2%)			
Follicular cell, hyperplasia	5 (8%)	18 (31%)	15 (25%)	18 (32%)
General Body System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Genital System				
Coagulating gland	(23)	(13)	(21)	(4)
Dilatation	23 (100%)	13 (100%)	21 (100%)	4 (100%)
Epididymis	(60)	(60)	(60)	(60)
Granuloma sperm	4 (7%)	1 (2%)	2 (3%)	3 (5%)
Inflammation, chronic			3 (5%)	1 (2%)
Penis		(1)		
Inflammation, chronic		1 (100%)		
Necrosis		1 (100%)		
Preputial gland	(27)	(36)	(24)	(21)
Degeneration, cystic	26 (96%)	33 (92%)	23 (96%)	21 (100%)
Inflammation, chronic	2 (7%)	5 (14%)	1 (4%)	1 (5%)
Prostate	(60)	(60)	(60)	(58)
Dilatation	2 (3%)	1 (2%)	2 (3%)	
Inflammation, chronic		2 (3%)	2 (3%)	1 (2%)
Seminal vesicle	(60)	(60)	(60)	(60)
Congestion				1 (2%)
Dilatation	35 (58%)	31 (52%)	36 (60%)	11 (18%)
Hemorrhage	2 (3%)	3 (5%)	1 (2%)	2 (3%)
Inflammation, chronic			2 (3%)	
Testes	(60)	(60)	(60)	(59)
Angiectasis	1 (2%)			
Degeneration				1 (2%)
Granuloma sperm	1 (2%)			
Mineralization			1 (2%)	1 (2%)
Germinal epithelium, degeneration	2 (3%)			6 (10%)
Hematopoietic System				
Bone marrow	(60)	(60)	(60)	(60)
Angiectasis	1 (2%)		1 (2%)	
Congestion	1 (2%)			
Hypercellularity	2 (3%)			1 (2%)
Myelofibrosis, focal		1 (2%)		
Lymph node	(9)	(5)	(1)	(1)
Angiectasis	1 (11%)		1 (100%)	
Inguinal, cyst				1 (100%)
Inguinal, hyperplasia		1 (20%)		
Inguinal, hyperplasia, lymphoid		2 (40%)		
Mediastinal, hyperplasia	3 (33%)			
Mediastinal, hyperplasia, lymphoid	1 (11%)			
Pancreatic, hyperplasia		1 (20%)		
Renal, hyperplasia	1 (11%)	1 (20%)		
Lymph node, mandibular	(57)	(59)	(58)	(56)
Hyperplasia	2 (4%)		2 (3%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	
Lymph node, mesenteric	(59)	(58)	(57)	(56)
Angiectasis	13 (22%)	23 (40%)	17 (30%)	13 (23%)
Hematopoietic cell proliferation	1 (2%)	4 (7%)	4 (7%)	
Hyperplasia	1 (2%)	1 (2%)		
Hyperplasia, lymphoid	10 (17%)	6 (10%)	9 (16%)	8 (14%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Hematopoietic System (continued)				
Spleen	(59)	(59)	(59)	(57)
Depletion cellular	2 (3%)	6 (10%)	5 (8%)	25 (44%)
Fibrosis	1 (2%)			1 (2%)
Hematopoietic cell proliferation	21 (36%)	14 (24%)	14 (24%)	11 (19%)
Hyperplasia, lymphoid	7 (12%)	12 (20%)	8 (14%)	7 (12%)
Thymus	(53)	(54)	(55)	(52)
Cyst	9 (17%)	3 (6%)	7 (13%)	5 (10%)
Hyperplasia, lymphoid		1 (2%)		
Mineralization		1 (2%)		
Epithelial cell, hyperplasia	1 (2%)			
Integumentary System				
Skin	(60)	(60)	(60)	(60)
Inflammation, chronic, focal	1 (2%)	2 (3%)	2 (3%)	
Ulcer		1 (2%)		
Epidermis, hyperplasia, focal		1 (2%)	1 (2%)	
Hair follicle, atrophy				1 (2%)
Subcutaneous tissue, abscess	1 (2%)			
Subcutaneous tissue, edema	1 (2%)		1 (2%)	
Subcutaneous tissue, hemorrhage	1 (2%)			
Subcutaneous tissue, inflammation, chronic		1 (2%)		
Musculoskeletal System				
Bone	(60)	(60)	(60)	(60)
Fibrous osteodystrophy	1 (2%)			
Hyperostosis				2 (3%)
Nervous System				
None				
Respiratory System				
Lung	(60)	(60)	(60)	(60)
Congestion		1 (2%)	1 (2%)	5 (8%)
Foreign body		1 (2%)		
Hemorrhage	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, macrophage	4 (7%)	1 (2%)	1 (2%)	
Infiltration cellular, mixed cell	1 (2%)	2 (3%)		
Inflammation, acute, focal				1 (2%)
Inflammation, chronic, focal	2 (3%)		1 (2%)	
Alveolar epithelium, hyperplasia	4 (7%)	4 (7%)	2 (3%)	1 (2%)
Artery, thrombosis	1 (2%)			
Bronchus, epithelium, hyperplasia		1 (2%)		
Nose	(60)	(60)	(60)	(59)
Inflammation, suppurative	1 (2%)			1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Special Senses System				
Eye	(2)		(1)	
Inflammation, chronic	1 (50%)			
Harderian gland	(10)	(3)	(3)	(1)
Inflammation, chronic	1 (10%)			
Urinary System				
Kidney	(60)	(58)	(59)	(57)
Atrophy, focal				1 (2%)
Congestion		1 (2%)		4 (7%)
Cyst	7 (12%)	4 (7%)	3 (5%)	1 (2%)
Hydronephrosis		1 (2%)	1 (2%)	
Nephropathy	51 (85%)	54 (93%)	55 (93%)	44 (77%)
Artery, inflammation, chronic			1 (2%)	1 (2%)
Pelvis, dilatation	3 (5%)	1 (2%)	1 (2%)	1 (2%)
Renal tubule, degeneration, hyaline	1 (2%)			
Renal tubule, dilatation	2 (3%)		1 (2%)	3 (5%)
Ureter				(1)
Dilatation				1 (100%)
Urethra	(1)	(2)		(3)
Angiectasis		1 (50%)		
Dilatation		1 (50%)		1 (33%)
Inflammation, acute		1 (50%)		
Inflammation, chronic	1 (100%)			2 (67%)
Bulbourethral gland, angiectasis		1 (50%)		
Urinary bladder	(59)	(59)	(58)	(59)
Calculus gross observation, multiple, greater than five				1 (2%)
Dilatation	3 (5%)	2 (3%)	2 (3%)	2 (3%)
Inflammation, chronic		3 (5%)	1 (2%)	37 (63%)
Artery, inflammation, chronic				1 (2%)
Transitional epithelium, hyperplasia	1 (2%)	3 (5%)	1 (2%)	17 (29%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF *t*-BUTYL ALCOHOL

TABLE D1 Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 202

TABLE D2 Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 206

TABLE D3 Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 242

TABLE D4a Historical Incidence of Liver Neoplasms in Untreated Female $B6C3F_1$ Mice 246

TABLE D4b Historical Incidence of Thyroid Gland Follicullar Cell Neoplasms in Untreated Female $B6C3F_1$ Mice 246

TABLE D5 Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 247

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Disposition Summary				
Animals initially in study	60	60	60	60
Early deaths				
Accidental deaths	1	3	2	2
Moribund	13	14	13	12
Natural deaths	10	8	4	4
Survivors				
Died last week of study			1	
Terminal sacrifice	36	35	40	42
Animals examined microscopically	60	60	60	60
Alimentary System				
Esophagus	(60)	(60)	(60)	(60)
Squamous cell carcinoma			1 (2%)	
Gallbladder	(58)	(59)	(58)	(56)
Intestine large, colon	(57)	(58)	(58)	(60)
Intestine small, duodenum	(58)	(57)	(56)	(60)
Polyp adenomatous		1 (2%)		
Intestine small, jejunum	(57)	(56)	(57)	(60)
Adenocarcinoma	2 (4%)			
Intestine small, ileum	(57)	(57)	(55)	(60)
Adenocarcinoma			1 (2%)	
Liver	(59)	(60)	(59)	(60)
Cholangiocarcinoma	1 (2%)	1 (2%)		1 (2%)
Hemangiosarcoma	2 (3%)			
Hepatocellular carcinoma	16 (27%)	18 (30%)	12 (20%)	8 (13%)
Hepatocellular carcinoma, multiple	9 (15%)	8 (13%)	10 (17%)	4 (7%)
Hepatocellular adenoma	17 (29%)	17 (28%)	16 (27%)	14 (23%)
Hepatocellular adenoma, multiple	12 (20%)	13 (22%)	15 (25%)	15 (25%)
Hepatocholangiocarcinoma		1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)		3 (5%)
Mesentery	(24)	(17)	(17)	(12)
Cholangiocarcinoma, metastatic, liver	1 (4%)	1 (6%)		1 (8%)
Fibrosarcoma		1 (6%)		
Hepatocholangiocarcinoma, metastatic, liver			1 (6%)	
Histiocytic sarcoma	1 (4%)			3 (25%)
Pancreas	(59)	(59)	(59)	(59)
Cholangiocarcinoma, metastatic, liver	1 (2%)			
Hemangioma				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma				2 (3%)
Salivary glands	(60)	(60)	(60)	(60)
Stomach, forestomach	(60)	(60)	(59)	(60)
Squamous cell papilloma		1 (2%)	2 (3%)	2 (3%)
Stomach, glandular	(60)	(60)	(59)	(59)
Cardiovascular System				
Heart	(60)	(60)	(60)	(60)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Endocrine System				
Adrenal cortex	(60)	(60)	(60)	(60)
Subcapsular, adenoma		1 (2%)	1 (2%)	
Subcapsular, carcinoma		1 (2%)		
Adrenal medulla	(60)	(60)	(60)	(60)
Pheochromocytoma benign			2 (3%)	
Islets, pancreatic	(59)	(59)	(59)	(59)
Adenoma	1 (2%)	1 (2%)		
Carcinoma				1 (2%)
Parathyroid gland	(48)	(56)	(57)	(50)
Pituitary gland	(56)	(57)	(60)	(60)
Pars distalis, adenoma	11 (20%)	18 (32%)	15 (25%)	18 (30%)
Thyroid gland	(58)	(60)	(59)	(59)
Bilateral, follicular cell, adenoma				1 (2%)
C-cell, adenoma				1 (2%)
Follicular cell, adenoma	2 (3%)	3 (5%)	2 (3%)	8 (14%)
General Body System				
Tissue NOS	(1)			
Genital System				
Ovary	(58)	(58)	(60)	(59)
Cystadenoma	2 (3%)		3 (5%)	3 (5%)
Histiocytic sarcoma	1 (2%)			
Luteoma	1 (2%)			
Teratoma benign			1 (2%)	
Teratoma NOS			1 (2%)	
Uterus	(60)	(60)	(59)	(59)
Granular cell tumor malignant				1 (2%)
Hemangioma				1 (2%)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	1 (2%)	1 (2%)		
Leiomyoma			1 (2%)	
Endometrium, polyp stromal	1 (2%)		1 (2%)	1 (2%)
Endometrium, polyp stromal, multiple, two				1 (2%)
Endometrium, sarcoma stromal		1 (2%)		
Hematopoietic System				
Bone marrow	(59)	(60)	(60)	(60)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	1 (2%)			2 (3%)
Lymph node	(19)	(12)	(6)	(13)
Bronchial, cholangiocarcinoma, metastatic, liver	1 (5%)			
Iliac, histiocytic sarcoma				1 (8%)
Mediastinal, cholangiocarcinoma, metastatic, liver	1 (5%)	1 (8%)		1 (8%)
Mediastinal, hepatocholangiocarcinoma, metastatic, liver		1 (8%)		
Mediastinal, histiocytic sarcoma		1 (8%)		1 (8%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Hematopoietic System (continued)				
Lymph node (continued)	(19)	(12)	(6)	(13)
Pancreatic, histiocytic sarcoma				1 (8%)
Renal, hemangiosarcoma		1 (8%)	1 (17%)	
Renal, histiocytic sarcoma				1 (8%)
Lymph node, mandibular	(59)	(58)	(59)	(57)
Histiocytic sarcoma		1 (2%)		1 (2%)
Lymph node, mesenteric	(56)	(59)	(57)	(57)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)		2 (4%)
Spleen	(59)	(60)	(59)	(59)
Hemangioma				1 (2%)
Hemangiosarcoma	1 (2%)	1 (2%)		1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)		3 (5%)
Thymus	(57)	(58)	(53)	(58)
Histiocytic sarcoma				1 (2%)
Thymocyte, thymoma benign		1 (2%)		1 (2%)
Integumentary System				
Mammary gland	(60)	(60)	(60)	(60)
Adenocarcinoma				1 (2%)
Skin	(60)	(60)	(60)	(60)
Subcutaneous tissue, fibrosarcoma		1 (2%)		2 (3%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, histiocytic sarcoma	1 (2%)			
Musculoskeletal System				
Skeletal muscle	(2)	(1)	(1)	(2)
Cholangiocarcinoma, metastatic, liver	1 (50%)	1 (100%)		1 (50%)
Hepatocholangiocarcinoma, metastatic, liver			1 (100%)	
Histiocytic sarcoma				1 (50%)
Nervous System				
Brain	(60)	(60)	(60)	(60)
Histiocytic sarcoma				1 (2%)
Meningioma malignant	1 (2%)			
Respiratory System				
Lung	(59)	(60)	(60)	(60)
Alveolar/bronchiolar adenoma	2 (3%)	3 (5%)	5 (8%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (3%)	2 (3%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple, two	1 (2%)			1 (2%)
Cholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		1 (2%)
Hepatocellular carcinoma, metastatic, liver	4 (7%)	3 (5%)	5 (8%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)			2 (3%)
Mediastinum, hepatocholangiocarcinoma, metastatic, liver		1 (2%)	1 (2%)	
Nose	(60)	(60)	(60)	(60)
Submucosa, hemangioma		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Special Senses System				
Ear		(1)		(1)
Pinna, hemangioma				1 (100%)
Harderian gland	(3)	(1)	(1)	(2)
Adenoma	1 (33%)	1 (100%)	1 (100%)	2 (100%)
Urinary System				
Kidney	(59)	(60)	(59)	(60)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)			1 (2%)
Renal tubule, adenoma				1 (2%)
Urinary bladder	(59)	(60)	(59)	(57)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(60)	(60)	(60)	(60)
Histiocytic sarcoma	3 (5%)	1 (2%)		3 (5%)
Lymphoma malignant lymphocytic	2 (3%)			
Lymphoma malignant mixed	15 (25%)	22 (37%)	21 (35%)	14 (23%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	54	54	55	53
Total primary neoplasms	107	120	115	111
Total animals with benign neoplasms	38	40	44	45
Total benign neoplasms	50	61	65	73
Total animals with malignant neoplasms	41	45	40	31
Total malignant neoplasms	57	59	49	38
Total animals with metastatic neoplasms	5	5	6	2
Total metastatic neoplasms	10	13	14	5
Total animals with uncertain neoplasms benign or malignant			1	
Total uncertain neoplasms			1	

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL

Number of Days on Study	0	1	2	3	3	4	4	5	5	5	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7
	1	7	5	3	3	6	7	5	6	8	8	9	0	4	5	5	5	0	0	0	1	2	2	2	3
	6	0	8	0	1	9	2	5	8	3	4	0	1	7	3	9	9	2	7	9	4	3	7	7	0
Carcass ID Number	2	2	2	2	2	2	2	2	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	6	9	9	6	8	8	4	7	6	0	9	4	5	8	9	4	6	9	9	7	4	5	6	8	5
	7	3	4	4	8	7	8	7	6	0	1	4	1	6	6	5	3	9	5	5	7	3	1	0	6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma														X											
Intestine small, ileum	+	+	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																			X						
Hemangiosarcoma			X													X									
Hepatocellular carcinoma										X	X			X	X	X						X	X	X	
Hepatocellular carcinoma, multiple																			X	X					
Hepatocellular adenoma							X				X						X			X	X				
Hepatocellular adenoma, multiple														X										X	
Histiocytic sarcoma										X															
Mesentery			+			+	+		+	+								+	+				+		+
Cholangiocarcinoma, metastatic, liver																			X						
Histiocytic sarcoma										X															
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver																			X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma													X												
Thyroid gland	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																		+							

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	730	730	730	730	730	730	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	257	271	272	273	274	276	241	242	243	246	249	250	252	254	255	258	259	260	262	265	268	269	270	278	279
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																	X								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Hemangiosarcoma																									
Hepatocellular carcinoma					X		X													X		X	X		
Hepatocellular carcinoma, multiple	X			X						X				X										X	
Hepatocellular adenoma						X	X				X	X	X				X				X			X	
Hepatocellular adenoma, multiple				X				X						X	X	X		X		X			X		
Histiocytic sarcoma																									
Mesentery	+					+		+		+	+				+	+	+			+	+				
Cholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+														
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X							X	X			X		X	X						X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								X	X
General Body System																									
Tissue NOS																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	281	282	283	284	285	289	290	292	297	298	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	+	+	+	+	58
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	57
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	58
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	58
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	58
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	57
Adenocarcinoma											2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	57
Liver	+	+	+	+	+	+	+	+	+	+	59
Cholangiocarcinoma											1
Hemangiosarcoma											2
Hepatocellular carcinoma	X			X					X		16
Hepatocellular carcinoma, multiple		X	X								9
Hepatocellular adenoma		X			X			X	X		17
Hepatocellular adenoma, multiple	X					X					12
Histiocytic sarcoma											1
Mesentery	+	+	+						+	+	24
Cholangiocarcinoma, metastatic, liver											1
Histiocytic sarcoma											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Cholangiocarcinoma, metastatic, liver											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tooth						+				+	3
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma											1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	56
Pars distalis, adenoma				X			X				11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	58
Follicular cell, adenoma											2
General Body System											
Tissue NOS											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	016	170	258	330	331	469	472	555	568	583	584	590	601	647	653	659	659	702	707	709	714	723	727	727	730
Carcass ID Number	267	293	294	264	288	287	248	277	266	300	291	244	251	286	296	245	263	299	295	275	247	253	261	280	256
Genital System																										
Clitoral gland												+														
Ovary	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma					X																					
Histiocytic sarcoma										X																
Luteoma																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Histiocytic sarcoma										X																
Endometrium, polyp stromal																					X					
Hematopoietic System																										
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X																
Lymph node			+			+	+		+			+						+	+				+	+	+
Bronchial, cholangiocarcinoma, metastatic, liver																			X							
Mediastinal, cholangiocarcinoma, metastatic, liver																			X							
Lymph node, mandibular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	A	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X																
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Histiocytic sarcoma																										
Thymus	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																										
Subcutaneous tissue, histiocytic sarcoma																									X	
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+													+							
Cholangiocarcinoma, metastatic, liver																			X							
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma malignant												X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	730	730	730	730	730	730	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	257	271	272	273	274	276	241	242	243	246	249	250	252	254	255	258	259	260	262	265	268	269	270	278	279
Genital System																									
Clitoral gland																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Cystadenoma																									
Histiocytic sarcoma																									
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Histiocytic sarcoma																									
Endometrium, polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node					+	+					+	+					+								+
Bronchial, cholangiocarcinoma, metastatic, liver																									
Mediastinal, cholangiocarcinoma, metastatic, liver																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																				
Histiocytic sarcoma	X																								
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma							X																		
Subcutaneous tissue, histiocytic sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Cholangiocarcinoma, metastatic, liver																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma malignant																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	281	282	283	284	285	289	290	292	297	298	Total Tissues/ Tumors
Genital System											
Clitoral gland											1
Ovary	+	+	+	+	+	+	+	+	+	+	58
Cystadenoma							X				2
Histiocytic sarcoma											1
Luteoma	X										1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Histiocytic sarcoma											1
Endometrium, polyp stromal											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	59
Histiocytic sarcoma											1
Lymph node		+	+		+						19
Bronchial, cholangiocarcinoma, metastatic, liver											1
Mediastinal, cholangiocarcinoma, metastatic, liver											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	59
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	56
Histiocytic sarcoma											1
Spleen	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma											1
Histiocytic sarcoma											1
Thymus	+	+	+	+	+	+	+	+	+	+	57
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	60
Skin	+	+	+	+	+	+	+	+	+	+	60
Subcutaneous tissue, hemangiosarcoma											1
Subcutaneous tissue, histiocytic sarcoma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											2
Cholangiocarcinoma, metastatic, liver											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Meningioma malignant											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	016	170	258	330	331	469	472	555	568	583	584	590	601	647	653	659	659	702	707	709	714	723	727	727	730
Carcass ID Number	267	293	294	264	288	287	248	277	266	300	291	244	251	286	296	245	263	299	295	275	247	253	261	280	256
Respiratory System																									
Lung	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple, two																								X	
Cholangiocarcinoma, metastatic, liver																			X						
Hepatocellular carcinoma, metastatic, liver										X				X	X					X					
Histiocytic sarcoma										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland						+																			
Adenoma																									
Urinary System																									
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Ureter																									
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X														X	
Lymphoma malignant lymphocytic														X				X							
Lymphoma malignant mixed						X	X		X														X		X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	730	730	730	730	730	730	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	257	271	272	273	274	276	241	242	243	246	249	250	252	254	255	258	259	260	262	265	268	269	270	278	279
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple, two																									
Cholangiocarcinoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Ureter																							+		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed			X		X	X			X		X					X					X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 0 mg/mL
(continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	281	282	283	284	285	289	290	292	297	298	Total Tissues/ Tumors
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	59
Alveolar/bronchiolar adenoma									X		2
Alveolar/bronchiolar carcinoma		X							X		2
Alveolar/bronchiolar carcinoma, multiple, two											1
Cholangiocarcinoma, metastatic, liver											1
Hepatocellular carcinoma, metastatic, liver											4
Histiocytic sarcoma											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Harderian gland							+			+	3
Adenoma							X				1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	59
Histiocytic sarcoma											1
Ureter											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Histiocytic sarcoma											1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											3
Lymphoma malignant lymphocytic											2
Lymphoma malignant mixed		X	X		X						15

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL

Number of Days on Study	072	310	365	054	055	570	776	577	610	616	628	633	635	674	684	696	696	704	700	709	710	715	724	727	727
Carcass ID Number	335	332	333	326	316	302	339	319	314	330	338	311	346	336	354	309	328	313	343	312	313	306	304	340	344
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma													X												
Hepatocellular carcinoma						X			X		X		X		X	X			X			X			
Hepatocellular carcinoma, multiple														X				X		X	X			X	
Hepatocellular adenoma												X								X					
Hepatocellular adenoma, multiple							X							X					X						X
Hepatocholangiocarcinoma								X																	
Histiocytic sarcoma																	X								
Mesentery				+			+			+	+		+		+		+		+				+	+	+
Cholangiocarcinoma, metastatic, liver													X												
Fibrosarcoma															X										
Pancreas	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver								X																	
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Subcapsular, carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X				X	X						X					X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	325	327	329	334	337	341	342	355	356	357	358	359	360	301	303	305	307	308	310	315	317	318	320	321	322
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																							X		
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Hepatocellular carcinoma		X	X	X											X	X	X							X	X
Hepatocellular carcinoma, multiple													X												
Hepatocellular adenoma	X		X	X	X	X			X			X		X					X		X				
Hepatocellular adenoma, multiple							X								X	X	X						X		
Hepatocholangiocarcinoma																									
Histiocytic sarcoma																									
Mesentery																+			+		+				
Cholangiocarcinoma, metastatic, liver																									
Fibrosarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+														
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																	X								
Subcapsular, carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma		X	X	X	X	X			X					X				X							X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma									X						X		X								
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	323	224	445	447	448	449	350	351	352	353	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	+	+	+	+	59
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	58
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	59
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	57
Polyp adenomatous											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	56
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	57
Liver	+	+	+	+	+	+	+	+	+	+	60
Cholangiocarcinoma											1
Hepatocellular carcinoma	X							X			18
Hepatocellular carcinoma, multiple				X						X	8
Hepatocellular adenoma			X				X	X	X	X	17
Hepatocellular adenoma, multiple	X			X	X	X					13
Hepatocholangiocarcinoma											1
Histiocytic sarcoma											1
Mesentery								+	+	+	17
Cholangiocarcinoma, metastatic, liver											1
Fibrosarcoma											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Squamous cell papilloma											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tooth											2
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Hepatocholangiocarcinoma, metastatic, liver											1
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Subcapsular, adenoma											1
Subcapsular, carcinoma									X		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma											1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	56
Pituitary gland	+	+	+	+	+	+	+	+	+	+	57
Pars distalis, adenoma		X		X				X	X		18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Follicular cell, adenoma											3
General Body System											
None											

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	0	3	3	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	7	1	6	0	5	7	7	7	1	1	2	3	3	7	8	9	9	0	0	0	1	1	2	2	2
	2	0	5	4	0	0	6	7	0	6	8	3	5	4	4	6	6	4	7	9	0	5	4	7	7
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	3	3	2	1	0	3	1	1	3	3	1	4	3	5	0	2	1	4	1	3	0	0	4	4
	5	2	3	6	6	2	9	9	4	0	8	1	6	6	4	9	8	3	3	2	1	6	4	0	4
Genital System																									
Clitoral gland																+									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Endometrium, sarcoma stromal																									
Vagina																					+				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+		+			+				+					+	+	+	+
Mediastinal, cholangiocarcinoma, metastatic, liver													X												
Mediastinal, hepatocholangiocarcinoma, metastatic, liver								X																	
Mediastinal, histiocytic sarcoma																	X								
Renal, hemangiosarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																	X								
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Thymocyte, thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+												
Cholangiocarcinoma, metastatic, liver													X												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma							X																		
Cholangiocarcinoma, metastatic, liver													X												
Hepatocellular carcinoma, metastatic, liver														X						X	X				
Hepatocholangiocarcinoma, metastatic, liver								X																	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	325	327	329	344	347	341	342	355	356	357	358	359	360	301	303	305	307	308	310	315	317	318	320	321	322
Genital System																									
Clitoral gland					+																				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Endometrium, sarcoma stromal										X															
Vagina																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+															+							
Mediastinal, cholangiocarcinoma, metastatic, liver																									
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																									
Mediastinal, histiocytic sarcoma																									
Renal, hemangiosarcoma																		X							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymocyte, thymoma benign				X																					
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Cholangiocarcinoma, metastatic, liver																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma														X											
Cholangiocarcinoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	
	5	5	5	5	5	5	5	5	5	5	
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	Total
	2	2	4	4	4	4	5	5	5	5	Tissues/
	3	4	5	7	8	9	0	1	2	3	Tumors
Genital System											
Clitoral gland											2
Ovary	+	+	+	+	+	+	+	+	+	+	58
Uterus	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Endometrium, sarcoma stromal											1
Vagina											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node		+							+		12
Mediastinal, cholangiocarcinoma, metastatic, liver											1
Mediastinal, hepatocholangiocarcinoma, metastatic, liver											1
Mediastinal, histiocytic sarcoma											1
Renal, hemangiosarcoma											1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	58
Histiocytic sarcoma											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	59
Histiocytic sarcoma											1
Spleen	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma				X							1
Histiocytic sarcoma											1
Thymus	+	+	+	+	+	+	+	+	+	+	58
Thymocyte, thymoma benign											1
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	60
Skin	+	+	+	+	+	+	+	+	+	+	60
Subcutaneous tissue, fibrosarcoma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											1
Cholangiocarcinoma, metastatic, liver											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma		X									3
Alveolar/bronchiolar carcinoma											2
Cholangiocarcinoma, metastatic, liver											1
Hepatocellular carcinoma, metastatic, liver											3
Hepatocholangiocarcinoma, metastatic, liver											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	072	310	365	504	550	570	576	577	610	616	628	633	635	674	684	696	696	704	707	709	710	715	724	727	727
Carcass ID Number	335	332	333	326	316	302	339	319	314	330	338	311	346	336	354	309	328	313	334	312	313	306	304	340	344
Respiratory System (continued)																										
Lung (continued)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinum, hepatocholangiocarcinoma, metastatic, liver								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Submucosa, hemangioma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear										+															
Harderian gland																								+	
Adenoma																								X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Lymphoma malignant mixed				X						X								X					X	X	X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	325	327	329	334	337	341	342	355	356	357	358	359	360	301	303	305	307	308	310	315	317	318	320	321	322
Respiratory System (continued)																									
Lung (continued)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Submucosa, hemangioma			X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant mixed	X		X	X					X	X	X	X		X		X				X	X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 5 mg/mL
(continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	323	224	345	447	448	449	350	351	352	353	Total Tissues/ Tumors
Respiratory System (continued)											
Lung (continued)	+	+	+	+	+	+	+	+	+	+	60
Mediastinum, hepatocholangiocarcinoma, metastatic, liver											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Submucosa, hemangioma											1
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Ear											1
Harderian gland											1
Adenoma											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Hepatocholangiocarcinoma, metastatic, liver											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Lymphoma malignant mixed		X	X	X					X	X	22

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL

Number of Days on Study	0	1	4	4	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	7	4	4	8	0	9	0	2	4	4	4	4	0	0	0	0	1	2	2	3	3	3	3	3	3
	9	0	0	8	6	1	7	5	5	6	6	7	2	2	7	7	0	7	8	3	4	4	4	4	4
Carcass ID Number	4	3	3	4	3	3	4	4	3	3	3	3	4	4	3	3	3	4	3	3	3	3	3	3	3
	0	6	8	1	7	9	1	1	9	6	8	7	1	1	6	7	6	1	9	7	6	6	6	6	6
	5	6	9	4	5	1	0	2	5	7	7	8	3	6	2	7	1	7	4	6	3	4	5	8	9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Gallbladder	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine large, rectum	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine large, cecum	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine small, ileum	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Adenocarcinoma																								X	
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma											X	X					X	X		X					
Hepatocellular carcinoma, multiple										X				X							X		X		
Hepatocellular adenoma			X			X			X	X		X	X					X							X
Hepatocellular adenoma, multiple											X												X		
Hepatocholangiocarcinoma																			X						
Mesentery						+		+		+			+			+			+			+		+	
Hepatocholangiocarcinoma, metastatic, liver																			X						
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																			X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel																				+					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																			X						
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																					X				
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X										X		X							
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734
Carcass ID Number	370	371	372	373	374	379	380	381	382	383	384	385	386	388	390	392	393	396	397	398	399	400	401	402	403
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																	X								
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma					X										X						X			X	
Hepatocellular carcinoma, multiple			X				X									X				X			X		
Hepatocellular adenoma								X					X							X	X		X		
Hepatocellular adenoma, multiple			X	X	X	X	X					X		X				X				X			X
Hepatocholangiocarcinoma																									
Mesentery				+				+							+	+	+			+		+	+		
Hepatocholangiocarcinoma, metastatic, liver																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma					X																				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth													+												
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma												X													
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X		X						X	X			X				X	X				X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma					X								X												

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	404	406	407	408	409	411	415	418	419	420	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Squamous cell carcinoma											1
Gallbladder	+	+	+	+	+	+	+	+	+	+	58
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	58
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	56
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	57
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	56
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	57
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	55
Adenocarcinoma											1
Liver	+	+	+	+	+	+	+	+	+	+	59
Hepatocellular carcinoma		X			X				X		12
Hepatocellular carcinoma, multiple										X	10
Hepatocellular adenoma					X		X	X			16
Hepatocellular adenoma, multiple			X	X					X		15
Hepatocholangiocarcinoma											1
Mesentery							+				17
Hepatocholangiocarcinoma, metastatic, liver											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Hepatocholangiocarcinoma, metastatic, liver											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	59
Squamous cell papilloma						X					2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Tooth											1
Cardiovascular System											
Blood vessel											1
Heart	+	+	+	+	+	+	+	+	+	+	60
Hepatocholangiocarcinoma, metastatic, liver											1
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Subcapsular, adenoma											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Pheochromocytoma benign											2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	57
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma			X		X						15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	59
Follicular cell, adenoma											2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	0	1	4	4	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	7	4	4	8	0	9	0	2	4	4	4	4	0	0	0	0	1	2	2	3	3	3	3	3	3
	9	0	0	8	6	1	7	5	5	6	6	7	2	2	7	7	0	7	8	3	4	4	4	4	4
Carcass ID Number	4	3	3	4	3	3	4	4	3	3	3	3	4	4	3	3	3	4	3	3	3	3	3	3	3
	0	6	8	1	7	9	1	1	9	6	8	7	1	1	6	7	6	1	9	7	6	6	6	6	6
	5	6	9	4	5	1	0	2	5	7	7	8	3	6	2	7	1	7	4	6	3	4	5	8	9
General Body System																									
None																									
Genital System																									
Clitoral gland															+						+				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma													X												
Teratoma benign	X																								
Teratoma NOS		X																							
Uterus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Endometrium, polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Lymph node													+	+	+	+									
Renal, hemangiosarcoma															X										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																			X						
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																			+						
Hepatocholangiocarcinoma, metastatic, liver																			X						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X		X	X										
Alveolar/bronchiolar carcinoma						X																			
Hepatocellular carcinoma, metastatic, liver											X							X		X	X				
Hepatocholangiocarcinoma, metastatic, liver																			X						
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734
Carcass ID Number	370	371	372	373	374	379	380	381	382	383	384	385	386	388	390	392	393	396	397	398	399	400	401	402	403
General Body System																									
None																									
Genital System																									
Clitoral gland																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma													X						X						
Teratoma benign																									
Teratoma NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																					X				
Endometrium, polyp stromal																							X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node																	+								
Renal, hemangiosarcoma																									
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Hepatocholangiocarcinoma, metastatic, liver																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver																									
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	0404	0406	0407	0408	0409	0411	0415	0418	0419	0420	Total Tissues/ Tumors
General Body System											
None											
Genital System											
Clitoral gland											2
Ovary	+	+	+	+	+	+	+	+	+	+	60
Cystadenoma											3
Teratoma benign											1
Teratoma NOS											1
Uterus	+	+	+	+	+	+	+	+	+	+	59
Leiomyoma											1
Endometrium, polyp stromal											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Lymph node										+	6
Renal, hemangiosarcoma											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	59
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	57
Hepatocholangiocarcinoma, metastatic, liver											1
Spleen	+	+	+	+	+	+	+	+	+	+	59
Thymus	+	+	+	+	+	+	+	+	+	+	53
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	60
Skin	+	+	+	+	+	+	+	+	+	+	60
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											1
Hepatocholangiocarcinoma, metastatic, liver											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma							X				5
Alveolar/bronchiolar carcinoma											1
Hepatocellular carcinoma, metastatic, liver										X	5
Hepatocholangiocarcinoma, metastatic, liver											1
Mediastinum, hepatocholangiocarcinoma, metastatic, liver											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	0	1	4	4	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	7	4	4	8	0	9	0	2	4	4	4	4	0	0	0	0	1	2	2	3	3	3	3	3	3
	9	0	0	8	6	1	7	5	5	6	6	7	2	2	7	7	0	7	8	3	4	4	4	4	4
Carcass ID Number	4	3	3	4	3	3	4	4	3	3	3	3	4	4	3	3	3	4	3	3	3	3	3	3	3
	0	6	8	1	7	9	1	1	9	6	8	7	1	1	6	7	6	1	9	7	6	6	6	6	6
	5	6	9	4	5	1	0	2	5	7	7	8	3	6	2	7	1	7	4	6	3	4	5	8	9
Special Senses System																									
Harderian gland																						+			
Adenoma																						X			
Urinary System																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																			X						
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																			X						
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed											X		X	X		X									X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734
Carcass ID Number	370	371	372	373	374	379	380	381	382	383	384	385	386	388	390	392	393	396	397	398	399	400	401	402	403	404
Special Senses System																										
Harderian gland																										
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed		X	X						X		X	X		X		X	X	X						X	X	

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 10 mg/mL
(continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	
	4	4	4	4	4	4	4	4	4	4	
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	Total
	0	0	0	0	0	1	1	1	1	2	Tissues/
	4	6	7	8	9	1	5	8	9	0	Tumors
Special Senses System											
Harderian gland											1
Adenoma											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	59
Hepatocholangiocarcinoma, metastatic, liver											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Hepatocholangiocarcinoma, metastatic, liver											1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed	X	X		X		X			X		21

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL

Number of Days on Study	064	074	224	472	595	632	644	651	651	668	675	687	695	702	707	726	727	727	729	729	729	729	729	729	730	730
Carcass ID Number	432	463	436	433	426	444	424	457	466	472	425	473	478	470	461	423	443	458	459	460	462	469	474	421	422
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma						X																			
Hepatocellular carcinoma								X						X	X										
Hepatocellular carcinoma, multiple																		X	X						
Hepatocellular adenoma							X				X										X	X		X	
Hepatocellular adenoma, multiple													X		X								X		
Histiocytic sarcoma									X															X	
Mesentery						+			+			+	+				+	+	+				+	+	
Cholangiocarcinoma, metastatic, liver						X																			
Histiocytic sarcoma									X															X	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																						X			
Histiocytic sarcoma																								X	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																		X							X
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Tooth											+														
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X				X	X			X	X	X				X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma															X										
C-cell, adenoma																								X	
Follicular cell, adenoma							X										X						X		X
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	427	428	429	430	431	434	435	437	438	439	440	441	442	445	446	447	448	449	450	451	452	453	454	455	456
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Hepatocellular carcinoma	X				X			X					X										X		
Hepatocellular carcinoma, multiple		X																			X				
Hepatocellular adenoma				X		X	X	X					X		X		X				X				X
Hepatocellular adenoma, multiple			X							X		X		X		X		X	X	X			X		
Histiocytic sarcoma			X																						
Mesentery			+															+			+				
Cholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma			X																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma			X																						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth			+																						
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X																	
Parathyroid gland	+	+	M	+	+	+	M	+	+	M	+	M	M	+	+	+	+	+	+	+	M	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X				X					X		X									X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma																									
C-cell, adenoma																									
Follicular cell, adenoma													X					X		X				X	
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	464	465	467	468	471	475	476	477	479	480	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	M	+	+	+	+	+	+	56
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	60
Liver	+	+	+	+	+	+	+	+	+	+	60
Cholangiocarcinoma											1
Hepatocellular carcinoma											8
Hepatocellular carcinoma, multiple											4
Hepatocellular adenoma											14
Hepatocellular adenoma, multiple					X		X	X			15
Histiocytic sarcoma											3
Mesentery											12
Cholangiocarcinoma, metastatic, liver											1
Histiocytic sarcoma											3
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Hemangioma											1
Histiocytic sarcoma											2
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Squamous cell papilloma											2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Tooth			+								3
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Carcinoma											1
Parathyroid gland	+	+	+	+	I	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma			X			X	X				18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	59
Bilateral, follicular cell, adenoma											1
C-cell, adenoma											1
Follicular cell, adenoma											8
General Body System											
None											

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	0	0	2	4	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	6	7	2	7	9	3	4	5	5	6	7	8	9	0	0	2	2	2	2	2	2	2	2	3	3
	4	4	4	2	5	2	6	1	1	8	5	7	5	2	7	6	7	7	9	9	9	9	9	0	0
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	3	6	3	3	2	4	2	5	6	7	2	7	7	7	6	2	4	5	5	6	6	6	7	2	2
	2	3	6	3	6	4	4	7	6	2	5	3	8	0	1	3	3	8	9	0	2	9	4	1	2
Genital System																										
Clitoral gland																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma							X										X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor malignant																						X				
Hemangioma																										
Endometrium, polyp stromal												X														
Endometrium, polyp stromal, multiple, two																										
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																X	
Lymph node				+		+			+	+		+	+				+		+							
Iliac, histiocytic sarcoma																										
Mediastinal, cholangiocarcinoma, metastatic, liver						X																				
Mediastinal, histiocytic sarcoma																										
Pancreatic, histiocytic sarcoma																										
Renal, histiocytic sarcoma																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Histiocytic sarcoma																										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Hemangioma										X																
Hemangiosarcoma															X											
Histiocytic sarcoma									X															X		
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																	
Thymocyte, thymoma benign																										
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma							X																			
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+			+																	
Cholangiocarcinoma, metastatic, liver						X																				
Histiocytic sarcoma									X																	
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	427	428	429	430	431	434	435	437	438	439	440	441	442	445	446	447	448	449	450	451	452	453	454	455	456
Genital System																										
Clitoral gland								+																		
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																										
Uterus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor malignant																										
Hemangioma								X																		
Endometrium, polyp stromal																										
Endometrium, polyp stromal, multiple, two															X											
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Lymph node	+		+															+		+					
Iliac, histiocytic sarcoma			X																						
Mediastinal, cholangiocarcinoma, metastatic, liver																									
Mediastinal, histiocytic sarcoma			X																						
Pancreatic, histiocytic sarcoma			X																						
Renal, histiocytic sarcoma			X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Histiocytic sarcoma			X																						
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									
Histiocytic sarcoma			X																						
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Histiocytic sarcoma																									
Thymocyte, thymoma benign																									X
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Cholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	464	465	467	468	471	475	476	477	479	480	Total Tissues/ Tumors
Genital System											
Clitoral gland											1
Ovary	+	+	+	+	+	+	+	+	+	+	59
Cystadenoma				X							3
Uterus	+	+	+	+	+	+	+	+	+	+	59
Granular cell tumor malignant											1
Hemangioma											1
Endometrium, polyp stromal											1
Endometrium, polyp stromal, multiple, two											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Lymph node									+		13
Iliac, histiocytic sarcoma											1
Mediastinal, cholangiocarcinoma, metastatic, liver											1
Mediastinal, histiocytic sarcoma											1
Pancreatic, histiocytic sarcoma											1
Renal, histiocytic sarcoma											1
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	57
Histiocytic sarcoma											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	57
Histiocytic sarcoma											2
Spleen	+	+	+	+	+	+	+	+	+	+	59
Hemangioma											1
Hemangiosarcoma											1
Histiocytic sarcoma											3
Thymus	+	+	+	+	+	+	+	+	+	+	58
Histiocytic sarcoma											1
Thymocyte, thymoma benign											1
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma					X						1
Skin	+	+	+	+	+	+	+	+	+	+	60
Subcutaneous tissue, fibrosarcoma											2
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											2
Cholangiocarcinoma, metastatic, liver											1
Histiocytic sarcoma											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	0	0	2	4	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	6	7	2	7	9	3	4	5	5	6	7	8	9	0	0	2	2	2	2	2	2	2	2	3	3
	4	4	4	2	5	2	6	1	1	8	5	7	5	2	7	6	7	7	9	9	9	9	9	0	0
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	3	6	3	3	2	4	2	5	6	7	2	7	7	7	6	2	4	5	5	6	6	6	7	2	2
	2	3	6	3	6	4	4	7	6	2	5	3	8	0	1	3	3	8	9	0	2	9	4	1	2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar carcinoma											X															
Alveolar/bronchiolar carcinoma, multiple, two																										
Cholangiocarcinoma, metastatic, liver						X																				
Hepatocellular carcinoma, metastatic, liver								X																		
Histiocytic sarcoma									X															X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear										+																
Pinna, hemangioma										X																
Eye																										
Harderian gland																										
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								X		
Renal tubule, adenoma																					X					
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X															X		
Lymphoma malignant mixed					X							X	X				X		X	X						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	427	428	429	430	431	434	435	437	438	439	440	441	442	445	446	447	448	449	450	451	452	453	454	455	456
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple, two													X												
Cholangiocarcinoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Pinna, hemangioma																									
Eye												+													
Harderian gland												+		+											
Adenoma												X		X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Lymphoma malignant mixed	X	X													X			X		X					X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol: 20 mg/mL
(continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	464	465	467	468	471	475	476	477	479	480	Total Tissues/ Tumors
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma	X										1
Alveolar/bronchiolar carcinoma											1
Alveolar/bronchiolar carcinoma, multiple, two											1
Cholangiocarcinoma, metastatic, liver											1
Hepatocellular carcinoma, metastatic, liver											1
Histiocytic sarcoma											2
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Ear											1
Pinna, hemangioma											1
Eye											1
Harderian gland											2
Adenoma											2
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Renal tubule, adenoma											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	57
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											3
Lymphoma malignant mixed						X			X		14

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Liver: Hepatocellular Adenoma				
Overall rate[a]	29/59 (49%)	30/60 (50%)	31/59 (53%)	29/60 (48%)
Adjusted rate[b]	66.8%	72.6%	62.6%	62.7%
Terminal rate[c]	22/36 (61%)	24/35 (69%)	23/41 (56%)	25/42 (60%)
First incidence (days)	472	576	440	646
Life table test[d]	P=0.187N	P=0.461	P=0.462N	P=0.276N
Logistic regression test[d]	P=0.335N	P=0.550N	P=0.556	P=0.366N
Cochran-Armitage test[d]	P=0.500N			
Fisher exact test[d]		P=0.536	P=0.427	P=0.537N
Liver: Hepatocellular Carcinoma				
Overall rate	25/59 (42%)	26/60 (43%)	22/59 (37%)	12/60 (20%)
Adjusted rate	53.9%	53.2%	46.4%	25.7%
Terminal rate	15/36 (42%)	13/35 (37%)	16/41 (39%)	8/42 (19%)
First incidence (days)	583	570	646	651
Life table test	P=0.001N	P=0.491	P=0.212N	P=0.004N
Logistic regression test	P=0.001N	P=0.568N	P=0.243N	P=0.003N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.532	P=0.354N	P=0.007N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	41/59 (69%)	44/60 (73%)	40/59 (68%)	36/60 (60%)
Adjusted rate	83.6%	86.1%	78.1%	73.2%
Terminal rate	28/36 (78%)	28/35 (80%)	30/41 (73%)	29/42 (69%)
First incidence (days)	472	570	440	646
Life table test	P=0.016N	P=0.350	P=0.219N	P=0.054N
Logistic regression test	P=0.026N	P=0.504	P=0.299N	P=0.061N
Cochran-Armitage test	P=0.099N			
Fisher exact test		P=0.397	P=0.500N	P=0.186N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/59 (3%)	3/60 (5%)	5/60 (8%)	1/60 (2%)
Adjusted rate	4.7%	8.1%	10.7%	2.4%
Terminal rate	1/36 (3%)	2/35 (6%)	2/41 (5%)	1/42 (2%)
First incidence (days)	584	715	647	729 (T)
Life table test	P=0.328N	P=0.496	P=0.267	P=0.451N
Logistic regression test	P=0.370N	P=0.517	P=0.233	P=0.491N
Cochran-Armitage test	P=0.391N			
Fisher exact test		P=0.508	P=0.226	P=0.494N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	3/59 (5%)	2/60 (3%)	1/60 (2%)	2/60 (3%)
Adjusted rate	8.0%	4.7%	1.8%	4.3%
Terminal rate	2/36 (6%)	1/35 (3%)	0/41 (0%)	1/42 (2%)
First incidence (days)	727	576	591	675
Life table test	P=0.342N	P=0.505N	P=0.263N	P=0.432N
Logistic regression test	P=0.393N	P=0.483N	P=0.290N	P=0.453N
Cochran-Armitage test	P=0.398N			
Fisher exact test		P=0.492N	P=0.303N	P=0.492N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/59 (7%)	5/60 (8%)	6/60 (10%)	3/60 (5%)
Adjusted rate	9.9%	12.6%	12.4%	6.7%
Terminal rate	2/36 (6%)	3/35 (9%)	2/41 (5%)	2/42 (5%)
First incidence (days)	584	576	591	675
Life table test	P=0.313N	P=0.495	P=0.444	P=0.422N
Logistic regression test	P=0.379N	P=0.522	P=0.392	P=0.470N
Cochran-Armitage test	P=0.393N			
Fisher exact test		P=0.511	P=0.382	P=0.491N
Ovary: Cystadenoma				
Overall rate	2/58 (3%)	0/58 (0%)	3/60 (5%)	3/59 (5%)
Adjusted rate	4.6%	0.0%	6.9%	6.4%
Terminal rate	1/35 (3%)	0/34 (0%)	2/41 (5%)	1/41 (2%)
First incidence (days)	331	–[e]	702	646
Life table test	P=0.288	P=0.239N	P=0.556	P=0.555
Logistic regression test	P=0.236	P=0.265N	P=0.502	P=0.494
Cochran-Armitage test	P=0.240			
Fisher exact test		P=0.248N	P=0.516	P=0.508
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	11/56 (20%)	18/57 (32%)	15/60 (25%)	18/60 (30%)
Adjusted rate	30.1%	44.8%	33.6%	39.7%
Terminal rate	10/35 (29%)	13/34 (38%)	12/41 (29%)	15/42 (36%)
First incidence (days)	601	577	591	675
Life table test	P=0.358	P=0.089	P=0.408	P=0.225
Logistic regression test	P=0.296	P=0.119	P=0.382	P=0.206
Cochran-Armitage test	P=0.210			
Fisher exact test		P=0.108	P=0.320	P=0.142
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	2/58 (3%)	3/60 (5%)	2/59 (3%)	9/59 (15%)
Adjusted rate	5.6%	8.6%	4.9%	19.6%
Terminal rate	2/36 (6%)	3/35 (9%)	2/41 (5%)	6/42 (14%)
First incidence (days)	729 (T)	729 (T)	729 (T)	646
Life table test	P=0.016	P=0.487	P=0.647N	P=0.052
Logistic regression test	P=0.011	P=0.487	P=0.647N	P=0.039
Cochran-Armitage test	P=0.007			
Fisher exact test		P=0.516	P=0.684N	P=0.028
All Organs: Hemangioma				
Overall rate	0/60 (0%)	1/60 (2%)	0/60 (0%)	3/60 (5%)
Adjusted rate	0.0%	2.9%	0.0%	6.6%
Terminal rate	0/36 (0%)	1/35 (3%)	0/41 (0%)	2/42 (5%)
First incidence (days)	–	729 (T)	–	668
Life table test	P=0.060	P=0.494	–	P=0.153
Logistic regression test	P=0.050	P=0.494	–	P=0.133
Cochran-Armitage test	P=0.044			
Fisher exact test		P=0.500	–	P=0.122

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
All Organs: Hemangiosarcoma				
Overall rate	5/60 (8%)	2/60 (3%)	1/60 (2%)	1/60 (2%)
Adjusted rate	11.9%	5.7%	2.2%	2.2%
Terminal rate	3/36 (8%)	2/35 (6%)	0/41 (0%)	0/42 (0%)
First incidence (days)	258	729 (T)	707	707
Life table test	P=0.047N	P=0.225N	P=0.089N	P=0.085N
Logistic regression test	P=0.062N	P=0.224N	P=0.113N	P=0.112N
Cochran-Armitage test	P=0.060N			
Fisher exact test		P=0.219N	P=0.103N	P=0.103N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	5/60 (8%)	3/60 (5%)	1/60 (2%)	4/60 (7%)
Adjusted rate	11.9%	8.6%	2.2%	8.7%
Terminal rate	3/36 (8%)	3/35 (9%)	0/41 (0%)	2/42 (5%)
First incidence (days)	258	729 (T)	707	668
Life table test	P=0.366N	P=0.366N	P=0.089N	P=0.424N
Logistic regression test	P=0.439N	P=0.360N	P=0.113N	P=0.507N
Cochran-Armitage test	P=0.443N			
Fisher exact test		P=0.359N	P=0.103N	P=0.500N
All Organs: Histiocytic Sarcoma				
Overall rate	3/60 (5%)	1/60 (2%)	0/60 (0%)	3/60 (5%)
Adjusted rate	7.2%	2.2%	0.0%	6.6%
Terminal rate	1/36 (3%)	0/35 (0%)	0/41 (0%)	2/42 (5%)
First incidence (days)	583	696	–	651
Life table test	P=0.583	P=0.308N	P=0.105N	P=0.594N
Logistic regression test	P=0.537	P=0.299N	P=0.118N	P=0.648N
Cochran-Armitage test	P=0.526			
Fisher exact test		P=0.309N	P=0.122N	P=0.660N
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rate	17/60 (28%)	22/60 (37%)	21/60 (35%)	14/60 (23%)
Adjusted rate	38.9%	53.0%	46.2%	29.9%
Terminal rate	11/36 (31%)	16/35 (46%)	17/41 (41%)	10/42 (24%)
First incidence (days)	469	504	646	595
Life table test	P=0.084N	P=0.214	P=0.442	P=0.205N
Logistic regression test	P=0.141N	P=0.256	P=0.347	P=0.289N
Cochran-Armitage test	P=0.211N			
Fisher exact test		P=0.218	P=0.278	P=0.339N
All Organs: Benign Neoplasms				
Overall rate	38/60 (63%)	40/60 (67%)	44/60 (73%)	45/60 (75%)
Adjusted rate	84.1%	84.8%	82.8%	88.2%
Terminal rate	29/36 (81%)	28/35 (80%)	32/41 (78%)	36/42 (86%)
First incidence (days)	331	576	79	646
Life table test	P=0.523	P=0.393	P=0.487	P=0.507
Logistic regression test	P=0.157	P=0.558	P=0.242	P=0.267
Cochran-Armitage test	P=0.081			
Fisher exact test		P=0.424	P=0.163	P=0.118

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol
(continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
All Organs: Malignant Neoplasms				
Overall rate	41/60 (68%)	45/60 (75%)	40/60 (67%)	31/60 (52%)
Adjusted rate	78.5%	81.8%	76.9%	57.2%
Terminal rate	25/36 (69%)	25/35 (71%)	29/41 (71%)	19/42 (45%)
First incidence (days)	258	504	591	595
Life table test	P=0.004N	P=0.326	P=0.238N	P=0.021N
Logistic regression test	P=0.003N	P=0.353	P=0.357N	P=0.026N
Cochran-Armitage test	P=0.012N			
Fisher exact test		P=0.272	P=0.500N	P=0.047N
All Organs: Benign or Malignant Neoplasms				
Overall rate	54/60 (90%)	54/60 (90%)	55/60 (92%)	53/60 (88%)
Adjusted rate	96.4%	96.4%	98.2%	94.6%
Terminal rate	34/36 (94%)	33/35 (94%)	40/41 (98%)	39/42 (93%)
First incidence (days)	258	504	79	595
Life table test	P=0.060N	P=0.538	P=0.247N	P=0.111N
Logistic regression test	P=0.281N	P=0.386N	P=0.629N	P=0.282N
Cochran-Armitage test	P=0.442N			
Fisher exact test		P=0.619N	P=0.500	P=0.500N

(T)Terminal sacrifice

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.

[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

[e] Not applicable; no neoplasms in animal group

Table D4a
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Chlorinated and Chloraminated Water	19/50	6/50	20/50
t-Butyl Alcohol	29/59	25/59	41/59
Overall Historical Incidence			
Total	110/239 (46.0%)	49/239 (20.5%)	132/239 (55.2%)
Standard deviation	15.0%	15.2%	19.3%
Range	26%-61%	8%-42%	32%-69%

[a] Data as of 31 March 1993

Table D4b
Historical Incidence of Thyroid Gland Follicullar Cell Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Chlorinated and Chloraminated Water	2/50	0/50	2/50
t-Butyl Alcohol	2/58	0/58	2/58
Overall Historical Incidence			
Total	8/238 (3.4%)	0/238 (0.0%)	8/238 (3.4%)
Standard deviation	2.2%		2.2%
Range	0%-5%		0%-5%

[a] Data as of 31 March 1993

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Disposition Summary				
Animals initially in study	60	60	60	60
Early deaths				
Accidental deaths	1	3	2	2
Moribund	13	14	13	12
Natural deaths	10	8	4	4
Survivors				
Terminal sacrifice	36	35	40	42
Died last day of study			1	
Animals examined microscopically	60	60	60	60
Alimentary System				
Gallbladder	(58)	(59)	(58)	(56)
Mucosa, hyperplasia		1 (2%)	1 (2%)	
Intestine small, duodenum	(58)	(57)	(56)	(60)
Inflammation, chronic			1 (2%)	
Perforation			1 (2%)	
Ulcer		1 (2%)	1 (2%)	
Intestine small, jejunum	(57)	(56)	(57)	(60)
Developmental malformation			1 (2%)	
Hyperplasia, lymphoid				2 (3%)
Liver	(59)	(60)	(59)	(60)
Basophilic focus	3 (5%)	1 (2%)		2 (3%)
Clear cell focus		5 (8%)	3 (5%)	
Eosinophilic focus	13 (22%)	14 (23%)	16 (27%)	20 (33%)
Fatty change	11 (19%)	8 (13%)	8 (14%)	6 (10%)
Fibrosis, focal	1 (2%)	1 (2%)	1 (2%)	
Focal cellular change				1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		5 (8%)
Hemorrhage	1 (2%)		1 (2%)	
Infarct	1 (2%)	2 (3%)	2 (3%)	
Infiltration cellular, mixed cell		1 (2%)		
Inflammation, focal	5 (8%)	2 (3%)	7 (12%)	3 (5%)
Mineralization, focal	1 (2%)			
Mixed cell focus	2 (3%)	5 (8%)	7 (12%)	4 (7%)
Necrosis			1 (2%)	
Necrosis, focal	2 (3%)	1 (2%)	2 (3%)	1 (2%)
Pigmentation	1 (2%)	3 (5%)	3 (5%)	
Tension lipidosis		1 (2%)	1 (2%)	
Thrombosis	1 (2%)			
Bile duct, hyperplasia			1 (2%)	
Centrilobular, atrophy		1 (2%)		
Centrilobular, fibrosis			1 (2%)	1 (2%)
Centrilobular, necrosis	2 (3%)		2 (3%)	1 (2%)
Mesentery	(24)	(17)	(17)	(12)
Cyst			1 (6%)	
Hemorrhage	1 (4%)	1 (6%)		
Inflammation, chronic	2 (8%)	2 (12%)	1 (6%)	
Fat, necrosis	14 (58%)	10 (59%)	12 (71%)	4 (33%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Alimentary System (continued)				
Pancreas	(59)	(59)	(59)	(59)
Atrophy, focal	3 (5%)	3 (5%)	1 (2%)	
Acinar cell, focal cellular change		1 (2%)		
Duct, dilatation		2 (3%)	1 (2%)	
Stomach, forestomach	(60)	(60)	(59)	(60)
Cyst				1 (2%)
Erosion	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic	4 (7%)	2 (3%)	1 (2%)	1 (2%)
Mineralization			1 (2%)	
Ulcer	2 (3%)		1 (2%)	1 (2%)
Mucosa, hyperplasia	3 (5%)	5 (8%)	5 (8%)	4 (7%)
Stomach, glandular	(60)	(60)	(59)	(59)
Angiectasis				1 (2%)
Erosion		1 (2%)	1 (2%)	
Mineralization			1 (2%)	
Pigmentation	1 (2%)		1 (2%)	
Ulcer			1 (2%)	
Mucosa, hyperplasia	2 (3%)			
Tooth	(3)	(2)	(1)	(3)
Incisor, dysplasia	3 (100%)	2 (100%)	1 (100%)	3 (100%)
Cardiovascular System				
Blood vessel			(1)	
Aorta, bacterium			1 (100%)	
Aorta, inflammation, focal, suppurative			1 (100%)	
Aorta, thrombosis			1 (100%)	
Heart	(60)	(60)	(60)	(60)
Hemorrhage	1 (2%)			
Inflammation, focal, suppurative			1 (2%)	
Mineralization, focal		1 (2%)		
Thrombosis		1 (2%)		
Endocrine System				
Adrenal cortex	(60)	(60)	(60)	(60)
Congestion		1 (2%)		
Focal cellular change	2 (3%)		3 (5%)	
Hematopoietic cell proliferation				1 (2%)
Subcapsular, hyperplasia, focal		3 (5%)		
Adrenal medulla	(60)	(60)	(60)	(60)
Congestion		1 (2%)		
Parathyroid gland	(48)	(56)	(57)	(50)
Cyst			1 (2%)	
Pituitary gland	(56)	(57)	(60)	(60)
Angiectasis	1 (2%)	2 (4%)		1 (2%)
Cyst		1 (2%)	1 (2%)	1 (2%)
Hemorrhage				2 (3%)
Pars distalis, focal cellular change	6 (11%)	6 (11%)	6 (10%)	2 (3%)
Pars distalis, hyperplasia, focal	1 (2%)	5 (9%)	5 (8%)	1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Endocrine System (continued)				
Thyroid gland	(58)	(60)	(59)	(59)
Degeneration, cystic	8 (14%)	9 (15%)	9 (15%)	4 (7%)
Inflammation, focal	1 (2%)			1 (2%)
C-cell, hyperplasia	2 (3%)			
Follicle, cyst		1 (2%)	1 (2%)	
Follicular cell, cyst		1 (2%)	1 (2%)	
Follicular cell, hyperplasia	19 (33%)	28 (47%)	33 (56%)	47 (80%)
General Body System				
None				
Genital System				
Clitoral gland	(1)	(2)	(2)	(1)
Degeneration, cystic	1 (100%)	2 (100%)	1 (50%)	1 (100%)
Ovary	(58)	(58)	(60)	(59)
Angiectasis	1 (2%)	2 (3%)	1 (2%)	1 (2%)
Hemorrhage	3 (5%)	1 (2%)	2 (3%)	
Necrosis	1 (2%)			
Thrombosis	1 (2%)			1 (2%)
Follicle, cyst	15 (26%)	13 (22%)	17 (28%)	12 (20%)
Periovarian tissue, hemorrhage				1 (2%)
Uterus	(60)	(60)	(59)	(59)
Angiectasis	1 (2%)	2 (3%)	1 (2%)	1 (2%)
Atrophy	1 (2%)			
Decidual reaction		1 (2%)		
Exudate	1 (2%)			
Hemorrhage	1 (2%)			
Hydrometra	20 (33%)	25 (42%)	19 (32%)	27 (46%)
Inflammation, suppurative	4 (7%)	1 (2%)	1 (2%)	3 (5%)
Endometrium, hyperplasia, cystic	58 (97%)	59 (98%)	58 (98%)	56 (95%)
Lymphatic, ectasia		1 (2%)		
Vagina		(1)		
Epithelium, metaplasia		1 (100%)		
Hematopoietic System				
Bone marrow	(59)	(60)	(60)	(60)
Angiectasis	1 (2%)			
Hypercellularity		1 (2%)		
Lymph node	(19)	(12)	(6)	(13)
Bronchial, hyperplasia, lymphoid	1 (5%)			
Iliac, angiectasis	1 (5%)			1 (8%)
Iliac, hematopoietic cell proliferation	1 (5%)			
Iliac, hyperplasia	1 (5%)	1 (8%)		1 (8%)
Inguinal, hyperplasia, lymphoid			1 (17%)	1 (8%)
Inguinal, hyperplasia, mast cell				1 (8%)
Mediastinal, angiectasis	1 (5%)	1 (8%)		
Mediastinal, hyperplasia			2 (33%)	
Mediastinal, hyperplasia, lymphoid	3 (16%)			
Renal, hematopoietic cell proliferation	1 (5%)			
Renal, hyperplasia	1 (5%)			1 (8%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Hematopoietic System (continued)				
Lymph node, mandibular	(59)	(58)	(59)	(57)
Hyperplasia	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	2 (3%)	1 (2%)	
Lymph node, mesenteric	(56)	(59)	(57)	(57)
Angiectasis			2 (4%)	2 (4%)
Hematopoietic cell proliferation		1 (2%)		1 (2%)
Hemorrhage			1 (2%)	
Hyperplasia	1 (2%)			
Hyperplasia, lymphoid	8 (14%)	10 (17%)	4 (7%)	4 (7%)
Hyperplasia, macrophage	1 (2%)			
Spleen	(59)	(60)	(59)	(59)
Depletion cellular	3 (5%)	2 (3%)		1 (2%)
Fibrosis	1 (2%)			
Hematopoietic cell proliferation	27 (46%)	25 (42%)	28 (47%)	20 (34%)
Hyperplasia, lymphoid	15 (25%)	18 (30%)	13 (22%)	18 (31%)
Pigmentation				1 (2%)
Thymus	(57)	(58)	(53)	(58)
Congestion	1 (2%)			
Cyst	2 (4%)			
Hyperplasia, lymphoid	3 (5%)	5 (9%)	3 (6%)	2 (3%)
Integumentary System				
Mammary gland	(60)	(60)	(60)	(60)
Dilatation		4 (7%)	4 (7%)	3 (5%)
Inflammation, chronic				1 (2%)
Skin	(60)	(60)	(60)	(60)
Inflammation, chronic, focal	1 (2%)	1 (2%)	1 (2%)	3 (5%)
Ulcer			1 (2%)	1 (2%)
Epidermis, hyperplasia, focal	1 (2%)			
Sebaceous gland, hyperplasia	1 (2%)			
Subcutaneous tissue, edema	2 (3%)	2 (3%)		
Subcutaneous tissue, hyperplasia, mast cell			1 (2%)	
Musculoskeletal System				
Bone	(60)	(60)	(60)	(60)
Fibrous osteodystrophy	30 (50%)	34 (57%)	34 (57%)	23 (38%)
Hyperostosis		1 (2%)	1 (2%)	
Nervous System				
Brain	(60)	(60)	(60)	(60)
Compression	1 (2%)	3 (5%)	6 (10%)	2 (3%)
Cyst epithelial inclusion				1 (2%)
Hemorrhage	2 (3%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Respiratory System				
Lung	(59)	(60)	(60)	(60)
Congestion	1 (2%)	2 (3%)		3 (5%)
Foreign body				3 (5%)
Hemorrhage	1 (2%)			4 (7%)
Hyperplasia, macrophage	1 (2%)	1 (2%)	2 (3%)	2 (3%)
Infiltration cellular, mixed cell		1 (2%)		
Inflammation, chronic, focal			1 (2%)	
Alveolar epithelium, hyperplasia		3 (5%)		2 (3%)
Nose	(60)	(60)	(60)	(60)
Foreign body				1 (2%)
Inflammation, suppurative	4 (7%)	1 (2%)		
Special Senses System				
Ear		(1)		(1)
Pinna, inflammation, chronic, focal		1 (100%)		
Pinna, ulcer		1 (100%)		
Eye				(1)
Atrophy				1 (100%)
Inflammation, chronic				1 (100%)
Urinary System				
Kidney	(59)	(60)	(59)	(60)
Cyst		1 (2%)		
Inflammation, suppurative				1 (2%)
Metaplasia, osseous			2 (3%)	2 (3%)
Nephropathy	40 (68%)	37 (62%)	36 (61%)	31 (52%)
Pelvis, dilatation		1 (2%)	2 (3%)	
Renal tubule, degeneration, hyaline	1 (2%)			
Renal tubule, vacuolization cytoplasmic		1 (2%)		
Urinary bladder	(59)	(60)	(59)	(57)
Inflammation, acute				1 (2%)
Inflammation, chronic				4 (7%)
Transitional epithelium, hyperplasia				3 (5%)

APPENDIX E
GENETIC TOXICOLOGY

Salmonella typhimurium Mutagenicity Test Protocol 254
Mouse Lymphoma Mutagenicity Test Protocol 254
Chinese Hamster Ovary Cell Cytogenetics Protocols 255
Mouse Peripheral Blood Micronucleus Test Protocol 256
Results 256
Table E1 Mutagenicity of *t*-Butyl Alcohol in *Salmonella typhimurium* 257
Table E2 Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by *t*-Butyl Alcohol 258
Table E3 Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *t*-Butyl Alcohol 260
Table E4 Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by *t*-Butyl Alcohol 262
Table E5 Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with *t*-Butyl Alcohol in Drinking Water for 13 Weeks 263

GENETIC TOXICOLOGY

Salmonella typhimurium Mutagenicity Test Protocol

Testing was performed as reported by Zeiger *et al.* (1987). *t*-Butyl alcohol was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of *t*-butyl alcohol. In the absence of toxicity, 10,000 μg/plate was selected as the high dose. All assays were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

Mouse Lymphoma Mutagenicity Test Protocol

The experimental protocol is presented in detail by McGregor *et al.* (1988). *t*-Butyl alcohol was supplied as a coded aliquot by Radian Corporation. The high dose of *t*-butyl alcohol was limited to 5,000 μg/mL. L5178Y mouse lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with *l*-glutamine, sodium pyruvate, pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring trifluorothymidine-resistant cells, subcultures were exposed to medium containing THMG (thymidine, hypoxanthine, methotrexate, and glycine) for 1 day, to medium containing THG (thymidine, hypoxanthine, and glycine) for 1 day, and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. All cells were incubated with *t*-butyl alcohol for 4 hours, at which time the medium plus *t*-butyl alcohol was removed and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (TFT) for selection of TFT-resistant ($TK^{-/-}$) cells; 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 for 10 to 12 days. The test was initially performed without S9. If a clearly positive response was not obtained, the test was repeated using freshly prepared S9 from the livers of Aroclor 1254-induced or non-induced male F344/N rats.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Caspary *et al.* (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for *t*-butyl alcohol to be considered

positive, i.e., capable of inducing TFT resistance. A single significant response led to a "questionable" conclusion, and the absence of both a trend and peak response resulted in a "negative" call.

Chinese Hamster Ovary Cell Cytogenetics Protocols

Testing was performed as reported by Galloway *et al.* (1987). *t*-Butyl alcohol was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least four doses of *t*-butyl alcohol; 5,000 μg/mL was selected as the high dose. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with *t*-butyl alcohol in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing *t*-butyl alcohol was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with *t*-butyl alcohol, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no *t*-butyl alcohol, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with *t*-butyl alcohol for 9 to 9.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with *t*-butyl alcohol and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 9.5 to 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. One hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P\leq0.05$) difference for one dose point and a significant trend ($P\leq0.015$) were considered weak evidence for a positive response; significant differences for two or

more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial cells were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

Mouse Peripheral Blood Micronucleus Test Protocol

A detailed discussion of this assay can be found in MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female $B6C3F_1$ mice at the end of the 13-week toxicity study. Smears were immediately prepared and fixed in absolute methanol, stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned at 630× or 1,000× magnification using a semi-automated image analysis system to determine the frequency of micronuclei in 10,000 normochromatic erythrocytes (NCEs) in up to 10 animals per dose group. The criteria of Schmid (1976) were used to define micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 510 nm UV illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell. In addition, the percentage of polychromatic erythrocytes (PCEs) among the total erythrocyte population was determined.

Results

t-Butyl alcohol (100 to 10,000 μg/plate) did not induce mutations in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537 with or without induced rat or hamster liver S9 (Table E1; Zeiger *et al.*, 1987). Results of a mouse lymphoma cell mutation test were also considered to be negative, although a small increase in mutant colonies was observed in a single trial at the highest dose tested (5,000 μg/mL) in the absence of S9 (Table E2; McGregor *et al.*, 1988). McGregor *et al.* (1988) presented an additional trial conducted without S9 that showed no increase in mutant colonies at any of the doses tested; that trial is not included in Table E2 because it did not meet quality control standards for the assay. The two trials conducted with S9 were clearly negative. In cytogenetic tests with cultured CHO cells, *t*-butyl alcohol, at doses up to 5,000 μg/mL, did not induce SCEs (Table E3) or Abs (Table E4), with or without S9. In the SCE test without S9, a weakly positive response was obtained in the first trial but it was not reproduced in the second trial. Neither trial conducted with S9 showed an increase in SCEs and the results of this test were considered negative. No cytotoxic effects were noted in the CHO cell experiments, with one exception. In the Abs test, a dose of 5,000 μg/mL in the second trial performed with S9 produced toxicity severe enough to allow only 13 cells to be analyzed for aberrations, rather than the usual 100 cells per dose point.

In vivo, no increase in the frequency of micronucleated NCEs was observed in male or female mice administered *t*-butyl alcohol in drinking water for 13 weeks (Table E5). In addition, no effect on the percentage of PCEs in the total erythrocyte population was noted, an indication that *t*-butyl alcohol was not toxic to bone marrow cells.

TABLE E1
Mutagenicity of *t*-Butyl Alcohol in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	121 ± 2.2	70 ± 6.2	136 ± 5.2	98 ± 3.4	133 ± 5.9	83 ± 2.2
	100	97 ± 13.9	69 ± 7.5	125 ± 15.0	83 ± 1.7	109 ± 8.1	85 ± 8.0
	333	98 ± 9.1	75 ± 2.9	113 ± 1.2	85 ± 4.5	134 ± 8.5	91 ± 3.5
	1,000	92 ± 9.0	92 ± 13.0	122 ± 8.7	85 ± 3.8	117 ± 4.9	84 ± 5.2
	3,333	110 ± 4.7	90 ± 6.9	116 ± 12.3	86 ± 4.9	114 ± 11.8	78 ± 4.3
	10,000	99 ± 9.0	86 ± 4.1	114 ± 3.8	75 ± 1.7	118 ± 8.1	82 ± 4.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		585 ± 40.5	495 ± 18.9	1,915 ± 139.3	2,124 ± 40.9	1,001 ± 112.9	1,372 ± 67.7
TA1535	0	5 ± 0.3	5 ± 0.9	7 ± 1.5	8 ± 2.1	7 ± 1.3	7 ± 3.5
	100	6 ± 0.3	8 ± 0.9	8 ± 0.9	9 ± 1.5	9 ± 0.3	11 ± 1.2
	333	4 ± 0.9	8 ± 0.9	6 ± 0.7	10 ± 1.7	6 ± 1.8	11 ± 2.6
	1,000	4 ± 0.7	6 ± 1.2	4 ± 0.9	11 ± 2.9	8 ± 0.9	7 ± 0.6
	3,333	4 ± 0.9	8 ± 1.0	7 ± 2.3	13 ± 3.2	6 ± 1.3	10 ± 0.9
	10,000	6 ± 1.0	9 ± 1.5	9 ± 1.5	13 ± 1.7	8 ± 0.3	11 ± 2.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		623 ± 19.8	526 ± 84.8	160 ± 11.1	86 ± 6.2	51 ± 0.7	90 ± 10.7
TA1537	0	3 ± 0.7	4 ± 1.2	8 ± 0.9	7 ± 0.6	11 ± 1.5	6 ± 2.5
	100	2 ± 1.9	7 ± 1.3	6 ± 2.0	7 ± 0.6	5 ± 1.3	6 ± 2.6
	333	3 ± 0.7	6 ± 1.8	5 ± 1.3	8 ± 1.2	4 ± 0.6	9 ± 3.2
	1,000	3 ± 1.2	6 ± 2.0	5 ± 0.3	10 ± 0.0	4 ± 1.3	7 ± 0.6
	3,333	2 ± 2.3	8 ± 0.6	5 ± 1.8	9 ± 4.4	4 ± 0.7	10 ± 1.5
	10,000	1 ± 0.9	6 ± 2.0	5 ± 2.0	6 ± 2.0	7 ± 0.6	10 ± 0.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		247 ± 99.6	101 ± 40.4	38 ± 3.0	39 ± 3.5	73 ± 11.8	108 ± 11.9
TA98	0	13 ± 2.5	13 ± 3.2	18 ± 3.8	18 ± 3.0	20 ± 0.3	20 ± 1.2
	100	12 ± 1.5	9 ± 2.3	19 ± 2.9	17 ± 4.4	16 ± 2.4	14 ± 0.3
	333	17 ± 1.9	8 ± 2.3	17 ± 3.5	12 ± 1.9	15 ± 1.5	15 ± 0.6
	1,000	9 ± 2.6	18 ± 3.7	14 ± 0.9	12 ± 1.7	21 ± 2.6	14 ± 2.9
	3,333	15 ± 5.8	10 ± 0.6	18 ± 0.7	15 ± 1.9	17 ± 1.5	13 ± 2.0
	10,000	10 ± 1.3	8 ± 0.6	17 ± 1.0	15 ± 2.3	18 ± 3.0	9 ± 1.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		234 ± 36.7	102 ± 7.9	1,442 ± 86.7	1,528 ± 84.1	836 ± 161.8	590 ± 70.0

[a] The detailed protocol and these data are presented in Zeiger *et al.* (1987).
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were 4-nitro-*o*-phenylenediamine (TA98), sodium azide (TA100 and TA1535), and 9-aminoacridine (TA1537). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by *t*-Butyl Alcohol[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Medium		62	100	144	78	
		60	96	160	90	
		67	111	207	103	
		54	93	157	98	92
Methyl methanesulfonate		20	22	369	605	
	15	23	25	337	499	552[d]
t-Butyl alcohol	1,000	55	112	153	93	
		62	91	185	100	96
	2,000	41	87	160	130	
		53	98	198	124	127
	3,000	62	81	257	139	
		55	90	191	115	127
	4,000	50	78	191	126	
		51	78	243	158	142
	5,000	58	75	275	157	
		52	71	227	146	152[d]
+S9						
Trial 1						
Medium		71	101	110	52	
		80	108	135	56	
		73	91	87	40	49
Methylcholanthrene		50	41	506	335	
	2.5	51	38	480	317	326[d]
t-Butyl alcohol	1,000	95	106	122	43	
		66	92	95	48	45
	2,000	77	101	96	42	
		92	108	124	45	43
	3,000	74	92	83	37	
		82	99	110	45	41
	4,000	71	115	110	52	
	5,000	81	102	100	41	
		84	118	97	39	40

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by *t*-Butyl Alcohol
(continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9 (continued)						
Trial 2						
Medium		103	105	67	22	
		93	104	34	12	
		70	95	37	18	
		92	96	52	19	18
Methylcholanthrene		77	33	531	231	
	2.5	67	38	461	231	231[d]
t-Butyl alcohol	2,000	62	105	61	33	
		80	94	44	18	26
	3,000	78	90	45	19	
		71	90	69	33	26
	4,000	79	95	33	14	
		80	90	47	20	17
	5,000	97	101	69	24	
		70	88	58	28	26

[a] Study performed at Inveresk Research International. The experimental protocol and these data are presented in McGregor *et al.* (1988).
[b] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/10^6 cells treated); MF = mutant fraction.
[c] Mean from three replicate plates of approximately 10^6 cells each
[d] Significant positive response ($P \leq 0.05$)

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *t*-Butyl Alcohol[a]

Compound	Dose µg/mL	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Trial 1								
Summary: Weakly positive								
Medium		50	1,039	419	0.40	8.4	26.0	
Mitomycin-C	0.001	50	1,039	661	0.63	13.2	26.0	57.76
	0.010	10	209	556	2.66	55.6	26.0	559.68
t-Butyl alcohol	160	50	1,045	444	0.42	8.9	26.0	5.36
	500	50	1,047	457	0.43	9.1	26.0	8.24
	1,600	50	1,046	486	0.46	9.7	26.0	15.21
	5,000	50	1,049	509	0.48	10.2	26.0	20.32*
					P<0.001[c]			
Trial 2								
Summary: Negative								
Medium		50	1,040	430	0.41	8.6	26.0	
Mitomycin-C	0.001	50	1,048	1,287	1.22	25.7	26.0	197.02
	0.010	10	210	674	3.20	67.4	26.0	676.26
t-Butyl alcohol	2,000	50	1,037	437	0.42	8.7	26.0	1.92
	3,000	50	1,039	433	0.41	8.7	26.0	0.79
	4,000	50	1,046	478	0.45	9.6	26.0	10.52
	5,000	50	1,040	453	0.43	9.1	26.0	5.35
					P=0.104			
+S9								
Trial 1								
Summary: Negative								
Medium		50	1,035	474	0.45	9.5	26.0	
Cyclophosphamide	0.3	50	1,041	606	0.58	12.1	26.0	27.11
	2.0	10	210	322	1.53	32.2	26.0	234.81
t-Butyl alcohol	160	50	1,037	459	0.44	9.2	26.0	−3.35
	500	50	1,048	438	0.41	8.8	26.0	−8.74
	1,600	50	1,040	452	0.43	9.0	26.0	−5.10
	5,000	50	1,047	400	0.38	8.0	26.0	−16.58
					P=0.994			

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *t*-Butyl Alcohol (continued)

Compound	Dose µg/mL	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
+S9 (continued)								
Trial 2								
Summary: Negative								
Medium		50	1,038	469	0.45	9.4	26.0	
Cyclophosphamide	0.3	50	1,044	622	0.59	12.4	26.0	31.86
	2.0	10	210	319	1.51	31.9	26.0	236.20
t-Butyl alcohol	2,000	50	1,047	505	0.48	10.1	26.0	6.75
	3,000	50	1,043	454	0.43	9.1	26.0	−3.66
	4,000	50	1,042	448	0.42	9.0	26.0	−4.85
	5,000	50	1,037	482	0.46	9.6	26.0	2.87
					P=0.715			

* Positive (≥20% increase over solvent control)
[a] Study performed at Environmental Health Research and Testing, Inc. A detailed description of the protocol is presented in Galloway *et al.* (1987). SCE = sister chromatid exchange; BrdU = bromodeoxyuridine.
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells.
[c] Significance of relative SCEs/chromosome tested by linear regression trend test vs. log of the dose

TABLE E4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by *t*-Butyl Alcohol[a]

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Trial 1 - Harvest time: 11.0 hours Summary: Negative					**Trial 1** - Harvest time: 11.5 hours Summary: Equivocal				
Medium					Medium				
	100	3	0.03	3.0		100	0	0.00	0.0
Mitomycin-C					Cyclophosphamide				
0.25	100	42	0.42	32.0	15	100	20	0.20	19.0
1.00	50	27	0.54	28.0	50	100	61	0.61	42.0
t-Butyl alcohol					*t*-Butyl alcohol				
160	100	3	0.03	3.0	160	100	4	0.04	4.0
500	100	4	0.04	4.0	500	100	1	0.01	1.0
1,600	100	1	0.01	1.0	1,600	100	3	0.03	3.0
5,000	100	3	0.03	3.0	5,000	100	6	0.06	6.0*
				P=0.651[b]					P=0.017
Trial 2 - Harvest time: 11.5 hours Summary: Negative					**Trial 2** - Harvest time: 12.0 hours Summary: Negative				
Medium					Medium				
	100	1	0.01	1.0		100	1	0.01	1.0
Mitomycin-C					Cyclophosphamide				
0.25	100	22	0.22	20.0	15	100	23	0.23	19.0
1.00	50	17	0.34	26.0	50	50	61	1.22	70.0
t-Butyl alcohol					*t*-Butyl alcohol				
1,600	100	5	0.05	5.0	1,600	100	4	0.04	4.0
3,000	100	3	0.03	3.0	3,000	100	2	0.02	2.0
4,000	100	0	0.00	0.0	4,000	100	2	0.02	2.0
5,000	100	5	0.05	5.0	5,000	13[c]	1	0.08	8.0
				P=0.360					P=0.334

* Positive (P≤0.05)
[a] Study performed at Environmental Health Research and Testing, Inc. The detailed description of the protocol is presented in Galloway *et al.* (1985, 1987). Abs = aberrations.
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose
[c] Due to severe toxicity, only 13 cells were scored at this concentration.

TABLE E5
Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with *t*-Butyl Alcohol in Drinking Water for 13 Weeks[a]

	Dose (ppm)	Percent Micronucleated NCE Cells[b]	PCE[b] (%)	Number of Mice
Male				
	0	0.09 ± 0.01	0.86 ± 0.14	8
	3,000	0.10 ± 0.01	1.03 ± 0.07	10
	5,000	0.07 ± 0.01	0.92 ± 0.16	10
	10,000	0.09 ± 0.02	0.68 ± 0.08	9
	20,000	0.08 ± 0.01	0.87 ± 0.10	9
	40,000	0.06 ± 0.03	0.52 ± 0.25	3
Urethane[c]	2,000	1.95 ± 0.07	1.79 ± 0.07	3
Female				
	0	0.06 ± 0.01	0.88 ± 0.13	9
	3,000	0.04 ± 0.01	0.68 ± 0.10	8
	5,000	0.05 ± 0.01	0.77 ± 0.16	10
	10,000	0.05 ± 0.01	0.88 ± 0.09	10
	20,000	0.07 ± 0.01	0.94 ± 0.08	9
	40,000	0.07 ± 0.01	0.81 ± 0.18	5

[a] Study performed at SRI, International. The detailed protocol is presented in MacGregor *et al.* (1990). 10,000 NCEs scored per animal.
[b] Data presented as mean ± standard error. NCE = normochromatic erythrocyte; PCE = polychromatic erythrocyte.
[c] Positive control; three male mice were exposed separately and were not part of the NTP toxicity study.

APPENDIX F
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol 266

TABLE F2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 268

TABLE F3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Drinking Water Study of *t*-Butyl Alcohol 269

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL
Male					
n	10	10	10	10	10
Necropsy body wt	361 ± 6	341 ± 7*	335 ± 5**	318 ± 6**	297 ± 4**
Brain					
Absolute	1.951 ± 0.012	1.959 ± 0.014	1.927 ± 0.017	1.893 ± 0.014**	1.853 ± 0.013**
Relative	5.42 ± 0.09	5.76 ± 0.09**	5.76 ± 0.10**	5.97 ± 0.08**	6.24 ± 0.08**
Heart					
Absolute	0.971 ± 0.022	0.950 ± 0.018	1.026 ± 0.038	0.914 ± 0.025	0.885 ± 0.018*
Relative	2.69 ± 0.05	2.80 ± 0.07	3.06 ± 0.09**	2.87 ± 0.04**	2.98 ± 0.04**
R. Kidney					
Absolute	1.285 ± 0.067	1.436 ± 0.023*	1.499 ± 0.041**	1.485 ± 0.037**	1.624 ± 0.035**
Relative	3.55 ± 0.17	4.22 ± 0.06**	4.47 ± 0.11**	4.67 ± 0.07**	5.47 ± 0.12**
Liver					
Absolute	13.600 ± 0.400	13.352 ± 0.488	13.693 ± 0.505	14.319 ± 0.563	14.711 ± 0.352
Relative	37.62 ± 0.66	39.07 ± 0.77	40.76 ± 0.98*	44.96 ± 1.15**	49.47 ± 0.78**
Lung					
Absolute	1.247 ± 0.050[b]	1.317 ± 0.038	1.408 ± 0.041*	1.250 ± 0.046	1.192 ± 0.027
Relative	3.42 ± 0.11[b]	3.87 ± 0.12**	4.21 ± 0.14**	3.93 ± 0.10**	4.01 ± 0.06**
R. Testis					
Absolute	1.438 ± 0.021	1.387 ± 0.035	1.446 ± 0.025	1.405 ± 0.029[b]	1.457 ± 0.062
Relative	3.99 ± 0.06	4.08 ± 0.13	4.32 ± 0.08	4.41 ± 0.08*[b]	4.90 ± 0.20**
Thymus					
Absolute	0.301 ± 0.016	0.301 ± 0.012	0.287 ± 0.014	0.269 ± 0.014	0.230 ± 0.012**
Relative	0.83 ± 0.04	0.88 ± 0.03	0.85 ± 0.04	0.84 ± 0.03	0.77 ± 0.04

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Female						
n	10	10	10	10	10	4
Necropsy body wt	186 ± 4	189 ± 3	187 ± 4	188 ± 3	184 ± 2	146 ± 16**
Brain						
Absolute	1.741 ± 0.018	1.777 ± 0.008	1.743 ± 0.018	1.741 ± 0.011	1.716 ± 0.017	1.628 ± 0.034**
Relative	9.40 ± 0.16	9.43 ± 0.16	9.36 ± 0.15	9.29 ± 0.10	9.32 ± 0.12	11.59 ± 1.34**
Heart						
Absolute	0.585 ± 0.010	0.623 ± 0.007	0.603 ± 0.017	0.608 ± 0.019	0.635 ± 0.017	0.525 ± 0.035
Relative	3.16 ± 0.06	3.31 ± 0.06	3.23 ± 0.05	3.24 ± 0.08	3.44 ± 0.07**	3.68 ± 0.26**
R. Kidney						
Absolute	0.671 ± 0.029	0.798 ± 0.016**	0.776 ± 0.012**	0.868 ± 0.022**	0.935 ± 0.014**	0.915 ± 0.018**
Relative	3.62 ± 0.15	4.23 ± 0.10*	4.17 ± 0.07*	4.62 ± 0.07**	5.08 ± 0.06**	6.56 ± 0.89**
Liver						
Absolute	6.011 ± 0.104	6.673 ± 0.195*	6.598 ± 0.152*	6.720 ± 0.208**	6.933 ± 0.135**	6.570 ± 0.480*
Relative	32.38 ± 0.29	35.29 ± 0.63*	35.41 ± 0.77*	35.83 ± 1.03**	37.64 ± 0.53**	45.80 ± 2.63**
Lung						
Absolute	0.850 ± 0.026	0.926 ± 0.024	0.932 ± 0.042	0.887 ± 0.019	0.918 ± 0.017	0.743 ± 0.052
Relative	4.58 ± 0.12	4.90 ± 0.11	4.98 ± 0.15	4.73 ± 0.06	4.99 ± 0.10	5.18 ± 0.30*
Thymus						
Absolute	0.204 ± 0.009	0.225 ± 0.011	0.213 ± 0.012	0.203 ± 0.010	0.210 ± 0.009	0.143 ± 0.024*
Relative	1.10 ± 0.05	1.19 ± 0.05	1.14 ± 0.06	1.08 ± 0.04	1.14 ± 0.05	0.95 ± 0.08

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No organ weights or organ-weight-to-body-weight ratios were calculated for males administered 40 mg/mL due to 100% mortality in this group.
[b] n=9

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
n	10	10	10	10
Male				
Necropsy body wt	485 ± 12	469 ± 10	471 ± 6	431 ± 12**
Brain				
Absolute	2.114 ± 0.020	2.109 ± 0.018	2.140 ± 0.019	2.134 ± 0.018
Relative	4.38 ± 0.11	4.51 ± 0.09	4.55 ± 0.05	4.98 ± 0.10**
R. Kidney				
Absolute	1.785 ± 0.056	1.850 ± 0.054	1.987 ± 0.057	1.903 ± 0.072
Relative	3.68 ± 0.09	3.96 ± 0.13	4.22 ± 0.13**	4.42 ± 0.15**
Liver				
Absolute	16.146 ± 0.615	16.517 ± 0.697	17.386 ± 0.637	16.263 ± 0.562
Relative	33.22 ± 0.80	35.47 ± 1.98	36.92 ± 1.37	37.77 ± 0.95*
Female				
Necropsy body wt	308 ± 5	290 ± 5	303 ± 7	267 ± 8**
Brain				
Absolute	1.913 ± 0.018	1.902 ± 0.027	1.925 ± 0.015	1.899 ± 0.013
Relative	6.23 ± 0.13	6.57 ± 0.10	6.39 ± 0.15	7.16 ± 0.20**
R. Kidney				
Absolute	1.074 ± 0.029	1.158 ± 0.033*	1.272 ± 0.025**	1.313 ± 0.028**
Relative	3.49 ± 0.08	3.99 ± 0.07**	4.21 ± 0.08**	4.95 ± 0.17**
Liver				
Absolute	10.306 ± 0.490	8.868 ± 0.240*	10.032 ± 0.255	9.724 ± 0.287
Relative	33.37 ± 1.19	30.55 ± 0.53	33.17 ± 0.68	36.48 ± 0.74*

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Male						
n	9	10	10	10	10	4
Necropsy body wt	38.6 ± 0.8	38.4 ± 1.0	38.7 ± 1.1	36.6 ± 0.8	33.8 ± 1.2**	26.1 ± 1.9**
Brain						
Absolute	0.458 ± 0.003	0.460 ± 0.006	0.464 ± 0.003	0.448 ± 0.004	0.453 ± 0.007	0.433 ± 0.010*
Relative	11.91 ± 0.28	12.06 ± 0.36	12.06 ± 0.33	12.30 ± 0.24	13.52 ± 0.45**	16.79 ± 1.04**
Heart						
Absolute	0.153 ± 0.004	0.160 ± 0.004	0.149 ± 0.005	0.153 ± 0.005	0.152 ± 0.004	0.115 ± 0.010**
Relative	3.99 ± 0.13	4.18 ± 0.12	3.85 ± 0.07	4.22 ± 0.21	4.52 ± 0.15*	4.41 ± 0.15
R. Kidney						
Absolute	0.278 ± 0.008	0.280 ± 0.010	0.286 ± 0.009	0.283 ± 0.008	0.296 ± 0.010	0.278 ± 0.015
Relative	7.22 ± 0.25	7.31 ± 0.24	7.39 ± 0.19	7.77 ± 0.25	8.79 ± 0.26**	10.68 ± 0.20**
Liver						
Absolute	1.641 ± 0.069	1.675 ± 0.046	1.630 ± 0.092	1.631 ± 0.022	1.644 ± 0.071	1.375 ± 0.177
Relative	42.53 ± 1.52	43.73 ± 1.02	41.82 ± 1.18	44.77 ± 0.92	48.69 ± 1.58**	52.04 ± 3.38**
Lung						
Absolute	0.170 ± 0.006	0.183 ± 0.010	0.176 ± 0.007	0.169 ± 0.008	0.177 ± 0.007	0.160 ± 0.009
Relative	4.41 ± 0.15	4.79 ± 0.27	4.58 ± 0.25	4.67 ± 0.30	5.25 ± 0.18*	6.17 ± 0.30**
R. Testis						
Absolute	0.115 ± 0.003	0.118 ± 0.003	0.122 ± 0.002	0.117 ± 0.003	0.118 ± 0.003	0.096 ± 0.010*[b]
Relative	2.99 ± 0.08	3.10 ± 0.09	3.18 ± 0.10	3.20 ± 0.11	3.50 ± 0.07**	3.87 ± 0.23**[b]
Thymus						
Absolute	0.042 ± 0.003	0.051 ± 0.003	0.042 ± 0.003	0.040 ± 0.001	0.046 ± 0.003	0.029 ± 0.005
Relative	1.09 ± 0.09	1.33 ± 0.07	1.09 ± 0.06	1.09 ± 0.04	1.36 ± 0.07*	1.08 ± 0.13

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Female						
n	10	9	10	10	9	6
Necropsy body wt	30.2 ± 1.1	31.1 ± 0.9	29.7 ± 0.6	30.5 ± 1.0	27.8 ± 0.6	24.9 ± 0.8**
Brain						
Absolute	0.469 ± 0.004	0.476 ± 0.006	0.467 ± 0.004	0.467 ± 0.005	0.453 ± 0.004*	0.457 ± 0.004
Relative	15.70 ± 0.56	15.40 ± 0.53	15.79 ± 0.23	15.45 ± 0.47	16.33 ± 0.34	18.42 ± 0.69**
Heart						
Absolute	0.126 ± 0.003	0.130 ± 0.006	0.123 ± 0.005	0.128 ± 0.004	0.130 ± 0.005	0.112 ± 0.003
Relative	4.20 ± 0.11	4.19 ± 0.19	4.14 ± 0.15	4.22 ± 0.16	4.70 ± 0.25	4.50 ± 0.16
R. Kidney						
Absolute	0.186 ± 0.006	0.186 ± 0.004	0.181 ± 0.004	0.187 ± 0.004	0.198 ± 0.005	0.208 ± 0.007**
Relative	6.19 ± 0.19	6.01 ± 0.26	6.11 ± 0.12	6.17 ± 0.20	7.11 ± 0.13**	8.36 ± 0.14**
Liver						
Absolute	1.404 ± 0.048	1.390 ± 0.054	1.337 ± 0.032	1.288 ± 0.037	1.381 ± 0.047	1.320 ± 0.068
Relative	46.73 ± 1.55	44.73 ± 1.42	45.11 ± 0.72	42.34 ± 0.64*	49.63 ± 1.42	52.80 ± 1.48**
Lung						
Absolute	0.173 ± 0.005	0.163 ± 0.009	0.159 ± 0.005	0.167 ± 0.008	0.173 ± 0.008	0.163 ± 0.008
Relative	5.77 ± 0.20	5.26 ± 0.27	5.39 ± 0.22	5.48 ± 0.21	6.24 ± 0.30	6.58 ± 0.36
Thymus						
Absolute	0.047 ± 0.002	0.054 ± 0.003	0.052 ± 0.003	0.052 ± 0.004	0.052 ± 0.002	0.047 ± 0.002
Relative	1.56 ± 0.07	1.74 ± 0.08	1.76 ± 0.09	1.70 ± 0.10	1.87 ± 0.09*	1.88 ± 0.10*

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=3

APPENDIX G
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE G1 Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol 272

TABLE G2 Hematology and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 276

TABLE G3 Hematology Data for Mice in the 13-Week Drinking Water Study of *t*-Butyl Alcohol 278

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Male						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)						
Day 15	39.2 ± 1.0	40.3 ± 1.3	39.9 ± 0.8	39.4 ± 0.9	40.7 ± 0.9	41.0 ± 0.8
Week 13	39.9 ± 0.7	40.5 ± 0.7	39.2 ± 0.4	39.1 ± 0.2	39.0 ± 0.4	–[b]
Hemoglobin (g/dL)						
Day 15	15.1 ± 0.4	15.6 ± 0.5	15.2 ± 0.3	15.1 ± 0.3	15.4 ± 0.2	15.7 ± 0.3
Week 13	15.6 ± 0.1	15.9 ± 0.2	15.4 ± 0.1	14.9 ± 0.1**	14.8 ± 0.1**	–
Erythrocytes ($10^6/\mu L$)						
Day 15	8.55 ± 0.20	8.77 ± 0.26	8.24 ± 0.17	8.44 ± 0.14	8.63 ± 0.15	8.80 ± 0.15
Week 13	9.17 ± 0.11	9.25 ± 0.14	8.96 ± 0.06	8.66 ± 0.07**	8.50 ± 0.06**	–
Mean cell volume (fL)						
Day 15	46.0 ± 0.5	45.8 ± 0.3	48.6 ± 0.5**	46.6 ± 0.5	47.1 ± 0.4	46.8 ± 0.4
Week 13	43.6 ± 0.4	43.9 ± 0.5	43.7 ± 0.5	45.1 ± 0.4*	45.9 ± 0.3**	–
Mean cell hemoglobin (pg)						
Day 15	17.6 ± 0.2	17.7 ± 0.1	18.4 ± 0.2**	17.9 ± 0.2	17.8 ± 0.1	17.8 ± 0.1
Week 13	17.0 ± 0.1	17.2 ± 0.1	17.2 ± 0.1	17.2 ± 0.1	17.5 ± 0.1**	–
Mean cell hemoglobin concentration (g/dL)						
Day 15	38.4 ± 0.3	38.7 ± 0.2	38.0 ± 0.2	38.4 ± 0.2	37.9 ± 0.3	38.2 ± 0.3
Week 13	39.1 ± 0.5	39.2 ± 0.5	39.4 ± 0.4	38.1 ± 0.3	38.0 ± 0.4	–
Platelets ($10^3/\mu L$)						
Day 15	488.6 ± 17.5	457.0 ± 14.5	516.1 ± 19.7	488.2 ± 12.9	478.1 ± 12.3	384.2 ± 17.8**
Week 13	613.0 ± 19.2	641.4 ± 21.0	648.1 ± 23.2	717.0 ± 20.3**	736.5 ± 21.6**	–
Reticulocytes ($10^6/\mu L$)						
Day 15	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0
Week 13	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	–
Leukocytes ($10^3/\mu L$)						
Day 15	4.32 ± 0.36	4.27 ± 0.24	4.50 ± 0.29	5.18 ± 0.22	5.18 ± 0.27	3.24 ± 0.33
Week 13	5.20 ± 0.26	5.50 ± 0.37	5.33 ± 0.31	5.96 ± 0.31	6.16 ± 0.42	–
Segmented neutrophils ($10^3/\mu L$)						
Day 15	0.37 ± 0.04	0.50 ± 0.11	0.39 ± 0.06	0.47 ± 0.09	0.65 ± 0.10	0.39 ± 0.05
Week 13	0.86 ± 0.11	0.99 ± 0.18	1.11 ± 0.11	0.95 ± 0.12	0.84 ± 0.09	–
Lymphocytes ($10^3/\mu L$)						
Day 15	3.86 ± 0.33	3.67 ± 0.20	4.00 ± 0.24	4.59 ± 0.22	4.47 ± 0.24	2.83 ± 0.33
Week 13	4.27 ± 0.27	4.49 ± 0.31	4.20 ± 0.31	4.92 ± 0.38	5.25 ± 0.42	–
Atypical lymphocytes ($10^3/\mu L$)						
Day 15	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.02 ± 0.02	0.01 ± 0.01	0.00 ± 0.00
Week 13	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.01	0.01 ± 0.01	–
Monocytes ($10^3/\mu L$)						
Day 15	0.04 ± 0.02	0.05 ± 0.01	0.05 ± 0.02	0.06 ± 0.02	0.04 ± 0.02	0.01 ± 0.01
Week 13	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.02	–
Eosinophils ($10^3/\mu L$)						
Day 15	0.05 ± 0.02	0.01 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Week 13	0.05 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.06 ± 0.02	0.04 ± 0.02	–
Nucleated erythrocytes ($10^3/\mu L$)						
Day 15	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.04 ± 0.01	0.02 ± 0.01	0.01 ± 0.01
Week 13	0.01 ± 0.01	0.02 ± 0.01	0.04 ± 0.02	0.05 ± 0.03	0.03 ± 0.01	–

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Male (continued)						
n	10	10	10	10	10	10
Clinical Chemistry						
Alkaline phosphatase (IU/L)						
Day 15	412 ± 16	392 ± 9	400 ± 11	373 ± 12	361 ± 9**	315 ± 14**
Week 13	188 ± 4[c]	188 ± 9[d]	167 ± 9[c]	184 ± 10[e]	215 ± 10[c]	–
Alanine aminotransferase (IU/L)						
Day 15	33 ± 1	33 ± 2	35 ± 2	33 ± 2	36 ± 1	43 ± 4
Week 13	50 ± 4	45 ± 2	42 ± 3	43 ± 2	56 ± 2	–
Sorbitol dehydrogenase (IU/L)						
Day 15	10 ± 1[c]	7 ± 1	7 ± 1[e]	15 ± 4	9 ± 1	8 ± 2
Week 13	9 ± 1	11 ± 2	12 ± 2	14 ± 1**	15 ± 2*	–
γ-Glutamyltransferase (IU/L)						
Day 15	0.0 ± 0.0	0.4 ± 0.4	0.5 ± 0.5	0.0 ± 0.0	1.2 ± 1.2	0.0 ± 0.0
Week 13	0.9 ± 0.6[c]	0.0 ± 0.0[d]	0.0 ± 0.0[c]	0.6 ± 0.6[e]	0.5 ± 0.5[c]	–
Bile acids (μmol/L)						
Day 15	7.33 ± 2.94[e]	21.56 ± 4.52**[e]	16.00 ± 3.41	14.60 ± 2.12	19.80 ± 4.12*	9.40 ± 1.93
Week 13	11.00 ± 3.12	8.60 ± 1.28	7.70 ± 1.22	13.40 ± 2.56	13.90 ± 3.17	–
Urinalysis						
Volume (mL/12 hr)						
Day 10	6.1 ± 0.8	4.3 ± 1.1[c]	5.9 ± 1.0	1.5 ± 0.3**	1.5 ± 0.4**[d]	1.3 ± 0.4**[d]
Week 13	5.6 ± 1.3[e]	5.5 ± 1.3	4.7 ± 0.4[e]	3.6 ± 0.3	3.1 ± 0.4	–
Specific gravity						
Day 10	1.020 ± 0.001	1.029 ± 0.007[c]	1.024 ± 0.002	1.060 ± 0.008**	1.080 ± 0.011**[e]	1.104 ± 0.019**[c]
Week 13	1.038 ± 0.005[e]	1.035 ± 0.003	1.043 ± 0.002	1.051 ± 0.002**	1.058 ± 0.003**	–
Female						
n	10	10	10	10	10	9
Hematology						
Hematocrit (%)						
Day 15	41.7 ± 0.8	41.8 ± 0.7	41.3 ± 0.5	42.2 ± 0.6	40.7 ± 0.5	43.0 ± 0.4
Week 13	40.2 ± 0.5	40.3 ± 0.3[e]	40.1 ± 0.4	39.7 ± 0.4	39.8 ± 0.3	39.6 ± 1.2[f]
Hemoglobin (g/dL)						
Day 15	15.2 ± 0.2	15.2 ± 0.2	15.0 ± 0.1	15.2 ± 0.2	14.8 ± 0.3	15.7 ± 0.2
Week 13	15.9 ± 0.2	15.6 ± 0.1[e]	15.7 ± 0.1	15.4 ± 0.1	15.3 ± 0.1	15.2 ± 0.5[f]
Erythrocytes (10^6/μL)						
Day 15	8.49 ± 0.15	8.43 ± 0.20	8.45 ± 0.09	8.46 ± 0.16	8.40 ± 0.10	8.84 ± 0.13
Week 13	8.48 ± 0.16	8.41 ± 0.05[e]	8.50 ± 0.05	8.33 ± 0.09	8.31 ± 0.06	8.47 ± 0.17[f]
Mean cell volume (fL)						
Day 15	49.0 ± 0.5	49.6 ± 0.5	49.0 ± 0.2	49.9 ± 0.5	48.3 ± 0.3	48.6 ± 0.6
Week 13	47.4 ± 0.8	47.9 ± 0.3[e]	47.1 ± 0.4	47.6 ± 0.5	47.9 ± 0.2	46.8 ± 0.6[f]
Mean cell hemoglobin (pg)						
Day 15	17.9 ± 0.1	18.1 ± 0.3	17.8 ± 0.2	18.0 ± 0.2	17.6 ± 0.2	17.8 ± 0.2
Week 13	18.7 ± 0.3	18.6 ± 0.1[e]	18.4 ± 0.1	18.6 ± 0.1	18.5 ± 0.1	17.9 ± 0.3[f]

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Female (continued)						
n	10	10	10	10	10	9
Hematology (continued)						
Mean cell hemoglobin concentration (g/dL)						
Day 15	36.5 ± 0.3	36.5 ± 0.3	36.4 ± 0.4	36.1 ± 0.3	36.3 ± 0.4	36.6 ± 0.2
Week 13	39.5 ± 0.6	38.8 ± 0.5[e]	39.1 ± 0.5	39.0 ± 0.4	38.5 ± 0.2	38.4 ± 0.5[f]
Platelets ($10^3/\mu L$)						
Day 15	454.7 ± 8.9	463.5 ± 9.2	465.5 ± 9.5	455.1 ± 12.5	452.4 ± 9.2[e]	356.6 ± 18.6**
Week 13	595.5 ± 13.3	629.2 ± 16.0[e]	563.2 ± 40.1	573.1 ± 20.6	578.7 ± 30.0	559.0 ± 39.3[f]
Reticulocytes ($10^6/\mu L$)						
Day 15	0.3 ± 0.0[e]	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0
Week 13	0.4 ± 0.1	0.2 ± 0.0[e]	0.2 ± 0.0[e]	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0[f]
Leukocytes ($10^3/\mu L$)						
Day 15	4.68 ± 0.45	4.35 ± 0.41	4.04 ± 0.34	4.46 ± 0.36	4.13 ± 0.43	3.86 ± 0.40
Week 13	3.63 ± 0.17	4.00 ± 0.19[e]	3.98 ± 0.15	3.92 ± 0.21	3.74 ± 0.27	3.05 ± 0.54[f]
Segmented neutrophils ($10^3/\mu L$)						
Day 15	0.40 ± 0.09	0.34 ± 0.08	0.29 ± 0.05	0.41 ± 0.04	0.43 ± 0.09	0.25 ± 0.05
Week 13	0.79 ± 0.10	0.81 ± 0.15[e]	0.69 ± 0.10	0.92 ± 0.19	0.79 ± 0.11	0.78 ± 0.12[f]
Lymphocytes ($10^3/\mu L$)						
Day 15	4.24 ± 0.39	3.98 ± 0.37	3.72 ± 0.32	3.97 ± 0.34	3.67 ± 0.37	3.58 ± 0.36
Week 13	2.81 ± 0.20	3.15 ± 0.17[e]	3.26 ± 0.16	2.97 ± 0.08	2.89 ± 0.22	2.25 ± 0.42[f]
Atypical lymphocytes ($10^3/\mu L$)						
Day 15	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 13	0.00 ± 0.00	0.00 ± 0.00[e]	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[f]
Monocytes ($10^3/\mu L$)						
Day 15	0.01 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.03 ± 0.02	0.01 ± 0.01	0.00 ± 0.00
Week 13	0.01 ± 0.01	0.00 ± 0.00[e]	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00[f]
Eosinophils ($10^3/\mu L$)						
Day 15	0.02 ± 0.02	0.02 ± 0.01	0.02 ± 0.01	0.05 ± 0.02	0.02 ± 0.01	0.03 ± 0.01
Week 13	0.02 ± 0.01	0.04 ± 0.02[e]	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.01[e]	0.01 ± 0.01[f]
Nucleated erythrocytes ($10^3/\mu L$)						
Day 15	0.02 ± 0.01	–	0.02 ± 0.01	0.02 ± 0.02	0.01 ± 0.01	–
Week 13	0.03 ± 0.01	0.04 ± 0.02[e]	0.00 ± 0.00[e]	0.04 ± 0.02	0.05 ± 0.02	0.03 ± 0.02[f]
Clinical Chemistry						
Alkaline phosphatase (IU/L)						
Day 15	366 ± 14	340 ± 13	312 ± 12**	322 ± 8[e]	313 ± 11*	317 ± 13
Week 13	186 ± 8[c]	169 ± 15[d]	168 ± 12[e]	155 ± 9[d]	160 ± 6[e]	212 ± 9[g]
Alanine aminotransferase (IU/L)						
Day 15	31 ± 1	30 ± 2	31 ± 2	31 ± 2	35 ± 2	46 ± 3**
Week 13	36 ± 2	45 ± 4*[e]	43 ± 2*	47 ± 5	50 ± 4**	63 ± 14*[f]
Sorbitol dehydrogenase (IU/L)						
Day 15	12 ± 3	10 ± 1	11 ± 1	9 ± 1	11 ± 1	10 ± 1
Week 13	8 ± 1	11 ± 2[e]	13 ± 1	14 ± 2	13 ± 3	13 ± 3[f]
γ-Glutamyltransferase (IU/L)						
Day 15	6.7 ± 1.2[e]	5.0 ± 1.8	3.2 ± 0.9	5.5 ± 1.8	5.8 ± 1.4	5.2 ± 1.2
Week 13	1.8 ± 1.2[c]	0.4 ± 0.4[d]	0.0 ± 0.0[c]	0.0 ± 0.0[d]	1.4 ± 0.7[e]	2.0 ± 2.0[g]
Bile acids (μmol/L)						
Day 15	9.90 ± 2.06	7.50 ± 1.63	10.90 ± 2.66	8.10 ± 1.52	13.00 ± 1.71	12.78 ± 2.17
Week 13	7.90 ± 1.37	9.33 ± 1.91[e]	8.10 ± 1.10	7.20 ± 1.12	8.70 ± 2.05	32.75 ± 9.28[f]

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Female (continued)						
n	10	10	10	10	10	9
Urinalysis						
Volume (mL/12 hr)						
Day 15	6.7 ± 0.7	6.0 ± 1.0	4.5 ± 1.3	2.4 ± 0.5**	2.1 ± 0.3**	1.8 ± 0.3**
Week 13	4.4 ± 1.0	4.6 ± 0.5	3.1 ± 0.8	0.9 ± 0.3**	1.1 ± 0.4**	0.6 ± 0.1**
Specific gravity						
Day 15	1.018 ± 0.001	1.021 ± 0.003[e]	1.021 ± 0.002[e]	1.053 ± 0.007**	1.049 ± 0.004**	1.060 ± 0.005**
Week 13	1.027 ± 0.006	1.023 ± 0.003[e]	1.030 ± 0.004	1.069 ± 0.009**[h]	1.065 ± 0.007**[h]	1.095 ± 0.007**[f]

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] No data were calculated at 13 weeks for 40 mg/mL males due to 100% mortality in this exposure group.
[c] n=8
[d] n=7
[e] n=9
[f] n=4
[g] n=3
[h] n=6

TABLE G2
Hematology and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	1.25 mg/mL	2.5 mg/mL	5 mg/mL
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	44.3 ± 0.5	43.2 ± 1.3	43.6 ± 0.6	43.9 ± 0.9
Hemoglobin (g/dL)	15.4 ± 0.2	14.8 ± 0.4	14.9 ± 0.2	15.0 ± 0.3
Erythrocytes ($10^6/\mu L$)	8.57 ± 0.10	8.38 ± 0.27	8.59 ± 0.10	8.56 ± 0.17
Mean cell volume (fL)	51.7 ± 0.4	51.7 ± 0.4	50.8 ± 0.4	51.4 ± 0.2
Mean cell hemoglobin (pg)	18.0 ± 0.2	17.8 ± 0.2	17.3 ± 0.1**	17.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)	34.8 ± 0.1	34.4 ± 0.3	34.2 ± 0.2	34.2 ± 0.2
Platelets ($10^3/\mu L$)	712.0 ± 21.8	740.3 ± 34.9	774.9 ± 24.3	721.2 ± 30.9
Leukocytes ($10^3/\mu L$)	6.01 ± 0.68	6.19 ± 0.42	6.07 ± 0.41	6.01 ± 0.65
Segmented neutrophils ($10^3/\mu L$)	2.05 ± 0.31	2.05 ± 0.22	2.00 ± 0.16	1.60 ± 0.13
Lymphocytes ($10^3/\mu L$)	3.77 ± 0.39	4.03 ± 0.25	3.95 ± 0.34	4.35 ± 0.66
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.18 ± 0.05	0.11 ± 0.02	0.15 ± 0.03	0.07 ± 0.02
Urinalysis				
Volume (mL/16 hr)	9.5 ± 1.7	5.6 ± 0.7	8.2 ± 1.8	8.5 ± 1.4
Specific gravity	1.026 ± 0.002	1.038 ± 0.004	1.035 ± 0.005	1.030 ± 0.004
pH	6.30 ± 0.11	6.25 ± 0.11	6.20 ± 0.11	6.00 ± 0.00

TABLE G2
Hematology and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL
Female				
n	10	9	10	10
Hematology				
Hematocrit (%)	41.8 ± 0.3	42.6 ± 0.7	43.6 ± 0.5*	42.1 ± 0.6
Hemoglobin (g/dL)	14.7 ± 0.1	15.0 ± 0.2	15.1 ± 0.2	14.6 ±0.2
Erythrocytes ($10^6/\mu L$)	8.00 ± 0.06	8.08 ± 0.12	8.14 ± 0.15	7.96 ± 0.11
Mean cell volume (fL)	52.3 ± 0.3	52.7 ± 0.3	53.7 ± 0.5*	52.8 ± 0.3
Mean cell hemoglobin (pg)	18.4 ± 0.1	18.6 ± 0.1	18.6 ± 0.2	18.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)	35.1 ± 0.2	35.3 ± 0.2	34.7 ± 0.2	34.7 ± 0.2
Platelets ($10^3/\mu L$)	675.9 ± 24.7[b]	622.2 ± 12.8	612.2 ± 16.1	629.7 ± 22.7
Leukocytes ($10^3/\mu L$)	1.94 ± 0.18[b]	2.02 ± 0.16	2.58 ± 0.16	2.25 ± 0.25
Segmented neutrophils ($10^3/\mu L$)	0.61 ± 0.06[b]	0.60 ± 0.04	0.68 ± 0.07	0.65 ± 0.09
Lymphocytes ($10^3/\mu L$)	1.30 ± 0.15[b]	1.37 ± 0.13	1.85 ± 0.11*	1.56 ± 0.19
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes ($10^3/\mu L$)	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.00 ± 0.00[b]	0.01 ± 0.01	0.01 ± 0.01	0.04 ± 0.02
n	10	10	10	10
Urinalysis				
Volume (mL/16 hr)	5.4 ± 0.8	4.6 ± 1.0	3.4 ± 0.3*	2.4 ± 0.3**
Specific gravity	1.027 ± 0.004	1.027 ± 0.003	1.042 ± 0.004**	1.057 ± 0.003**
pH	6.55 ± 0.09	6.35 ± 0.08	6.25 ± 0.08*	6.05 ± 0.05**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

TABLE G3
Hematology Data for Mice in the 13-Week Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Male						
n	9	10	10	9	10	4
Hematocrit (%)	40.0 ± 0.8	40.6 ± 0.7	40.5 ± 0.6	41.8 ± 0.7	42.5 ± 1.1	44.2 ± 1.2**
Hemoglobin (g/dL)	15.1 ± 0.1	15.3 ± 0.2	15.4 ± 0.1	15.5 ± 0.2	15.8 ± 0.2*	16.8 ± 0.6**
Erythrocytes ($10^6/\mu L$)	9.91 ± 0.12	9.92 ± 0.09	10.13 ± 0.07	10.14 ± 0.08	10.23 ± 0.15	10.88 ± 0.49*
Mean cell volume (fL)	40.3 ± 0.6	41.0 ± 0.7	39.9 ± 0.6	41.3 ± 0.4	41.6 ± 0.7	40.5 ± 1.0
Mean cell hemoglobin (pg)	15.2 ± 0.1	15.5 ± 0.1	15.2 ± 0.1	15.3 ± 0.1	15.4 ± 0.1	15.4 ± 0.2
Mean cell hemoglobin concentration (g/dL)	37.9 ± 0.5	37.9 ± 0.7	38.1 ± 0.5	37.3 ± 0.3	37.3 ± 0.8	37.9 ± 0.4
Platelets ($10^3/\mu L$)	846.3 ± 23.2	809.1 ± 24.8	866.7 ± 18.6	852.1 ± 23.6	811.2 ± 19.4	865.1 ± 41.1
Reticulocytes ($10^6/\mu L$)	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0[b]	0.4 ± 0.1
Leukocytes ($10^3/\mu L$)	1.46 ± 0.24	1.49 ± 0.36	1.85 ± 0.40	1.13 ± 0.15	2.06 ± 0.32	4.48 ± 2.25
Segmented neutrophils ($10^3/\mu L$)	0.24 ± 0.06	0.19 ± 0.04	0.19 ± 0.03	0.23 ± 0.06	0.32 ± 0.04	2.84 ± 2.39*
Bands ($10^3/\mu L$)	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.03 ± 0.01	0.07 ± 0.05
Lymphocytes ($10^3/\mu L$)	1.19 ± 0.18	1.27 ± 0.31	1.61 ± 0.35	0.89 ± 0.09	1.68 ± 0.28	1.54 ± 0.62
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.03 ± 0.01	0.03 ± 0.03

TABLE G3
Hematology Data for Mice in the 13-Week Drinking Water Study of *t*-Butyl Alcohol (continued)

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Female						
n	9	9	10	10	9	5
Hematocrit (%)	41.4 ± 0.7	41.4 ± 0.7	42.7 ± 0.7	40.6 ± 0.7	42.6 ± 0.5	43.0 ± 0.9
Hemoglobin (g/dL)	15.3 ± 0.1	15.3 ± 0.1	15.5 ± 0.1	15.5 ± 0.1	15.7 ± 0.1*	15.3 ± 0.4
Erythrocytes ($10^6/\mu L$)	9.81 ± 0.06	9.81 ± 0.09	9.97 ± 0.07	9.90 ± 0.11	10.08 ± 0.10*	10.18 ± 0.15*
Mean cell volume (fL)	42.3 ± 0.7	42.3 ± 0.7	42.9 ± 0.7	41.2 ± 0.6	42.3 ± 0.8	42.2 ± 1.4
Mean cell hemoglobin (pg)	15.6 ± 0.1	15.6 ± 0.1	15.5 ± 0.1	15.7 ± 0.1	15.6 ± 0.1	15.1 ± 0.5
Mean cell hemoglobin concentration (g/dL)	37.0 ± 0.6	37.0 ± 0.6	36.3 ± 0.6	38.2 ± 0.5	36.9 ± 0.6	35.6 ± 1.1
Platelets ($10^3/\mu L$)	820.2 ± 32.7	817.3 ± 30.9	772.7 ± 20.2	772.5 ± 29.1	740.2 ± 35.5	725.0 ± 27.8
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.3 ± 0.0[c]	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.1[c]	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	2.06 ± 0.31	2.04 ± 0.19	2.14 ± 0.32	2.01 ± 0.53	2.51 ± 0.42	2.38 ± 0.46
Segmented neutrophils ($10^3/\mu L$)	0.29 ± 0.05	0.31 ± 0.05	0.31 ± 0.06	0.14 ± 0.04	0.31 ± 0.09	0.46 ± 0.09
Bands ($10^3/\mu L$)	0.01 ± 0.00	0.00 ± 0.00	0.01 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.03 ± 0.02
Lymphocytes ($10^3/\mu L$)	1.74 ± 0.28	1.72 ± 0.17	1.80 ± 0.26	1.84 ± 0.49	2.16 ± 0.35	1.88 ± 0.46
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.04 ± 0.02	0.02 ± 0.01

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9
[c] n=8

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE H1 Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol 282
TABLE H2 Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Drinking Water Study of *t*-Butyl Alcohol 283

TABLE H1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Male						
n	10	10	10	10	10	0
Weights (g)						
Right cauda	0.205 ± 0.008	0.195 ± 0.011	0.211 ± 0.006	0.205 ± 0.003[b]	0.199 ± 0.004	–[c]
Right epididymis	0.415 ± 0.011	0.420 ± 0.009	0.418 ± 0.008	0.397 ± 0.015[b]	0.395 ± 0.007	–
Right testis	1.44 ± 0.02	1.42 ± 0.03	1.45 ± 0.02	1.40 ± 0.03[b]	1.46 ± 0.06	–
Epididymal spermatozoal measurements						
Motility (%)	79.44 ± 0.64	79.44 ± 0.37	78.75 ± 0.46	79.00 ± 0.36	79.82 ± 0.75	–
Abnormality (%)	0.640 ± 0.111	0.860 ± 0.300	0.680 ± 0.120	1.240 ± 0.350	1.040 ± 0.202	–
Concentration (10^6/g cauda epididymal tissue)	523 ± 33	543 ± 46	509 ± 34	457 ± 19	513 ± 24[b]	–
Female[d]						
n	10	10	10	10	8[e]	0[f]
Estrous cycle length (days)	5.10 ± 0.18	5.00 ± 0.21	4.90 ± 0.18	5.10 ± 0.18	5.50 ± 0.19	–
Estrous stages (% of cycle)						
Diestrus	35.7	32.9	35.7	34.3	38.6	71.4
Proestrus	15.7	18.6	17.1	17.1	20.0	7.1
Estrus	24.3	27.1	27.1	25.7	18.6	14.3
Metestrus	24.3	21.4	20.0	22.9	22.9	7.1

[a] Data are presented as mean ± standard error. Differences from the control group for all study parameters are not significant by Dunn's test.
[b] n=9
[c] No data calculated due to 100% mortality in this exposure group.
[d] Evidence suggests that females in the 40 mg/mL group differ significantly ($P<0.01$, Wilks' Criterion) from the control females in the relative length of time spent in estrous stages. Females in this exposure group spent more time in diestrus and less time in proestrus, estrus, and metestrus than control females.
[e] Estrous cycle was longer than 7 days or was unclear in 2 of 10 animals.
[f] Among four animals, three had a cycle length that was longer than 7 days or was unclear, and one animal exhibited no cycle.

TABLE H2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Drinking Water Study of *t*-Butyl Alcohol[a]

	0 mg/mL	2.5 mg/mL	5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL
Male						
n	9	10	10	10	10	4
Weights (g)						
Right cauda	0.022 ± 0.002	0.023 ± 0.001	0.028 ± 0.002	0.023 ± 0.002	0.024 ± 0.002	0.018 ± 0.001
Right epididymis	0.046 ± 0.002	0.049 ± 0.002	0.051 ± 0.003	0.049 ± 0.002	0.049 ± 0.002	0.037 ± 0.004
Right testis	0.115 ± 0.003	0.118 ± 0.003	0.122 ± 0.002	0.117 ± 0.003	0.118 ± 0.003	0.101 ± 0.009
Epididymal spermatozoal measurements						
Motility (%)	77.80 ± 0.61	79.08 ± 0.71	77.32 ± 0.52	78.01 ± 0.55	78.39 ± 0.81	75.70 ± 1.05
Abnormality (%)	0.911 ± 0.192	0.840 ± 0.142	0.920 ± 0.144	0.980 ± 0.230	0.840 ± 0.107	1.000 ± 0.216
Concentration (10^6/g cauda epididymal tissue)	951 ± 69	898 ± 49	830 ± 100	978 ± 72	810 ± 54	1,162 ± 106
Female						
n	10	9	9[b]	9[c]	8[d]	2[e]
Estrous cycle length (days)	3.90 ± 0.10	4.11 ± 0.11	4.11 ± 0.11	4.11 ± 0.11	4.13 ± 0.13	5.00 ± 0.00**
Estrous stages (% of cycle)						
Diestrus	21.4	25.4	22.9	30.0	33.3	31.0
Proestrus	24.3	22.2	20.0	22.9	20.6	14.3
Estrus	34.3	28.6	30.0	28.6	25.4	45.2
Metestrus	20.0	23.8	27.1	17.1	20.6	9.5
Uncertain diagnoses	0.0	0.0	0.0	1.4	0.0	0.0

** Significantly different ($P \leq 0.01$) from the control group by Dunn's test
[a] Data are presented as mean ± standard error.
[b] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.
[c] No estrous cycle in 1 of 10 animals
[d] No estrous cycle in 1 of 9 animals
[e] Estrous cycle was longer than 7 days or was unclear in 4 of 6 animals.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization 286
Preparation and Analysis of Dose Formulations 287
Figure I1 Infrared Absorption Spectrum of *t*-Butyl Alcohol 288
Figure I2 Nuclear Magnetic Resonance Spectrum of *t*-Butyl Alcohol 289
Table I1 Preparation and Storage of Dose Formulations in the Drinking Water Studies of *t*-Butyl Alcohol 290
Table I2 Results of Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week Drinking Water Studies of *t*-Butyl Alcohol 291
Table I3 Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of *t*-Butyl Alcohol 292
Table I4 Results of Referee Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Drinking Water Studies of *t*-Butyl Alcohol 297

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization

t-Butyl alcohol was obtained from FBC Chemical Corporation (Lancaster, NY) in one lot (F112784). Lot F112784 was used during the 13-week and 2-year drinking water studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the *t*-butyl alcohol studies are on file at the National Institute of Environmental Health Sciences.

All lots of the chemical, a clear colorless liquid, were identified as *t*-butyl alcohol by infrared, ultraviolet/visible, and nuclear magnetic resonance (NMR) spectroscopy. All spectra were consistent with those expected for the structure, and the infrared and NMR spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) of *t*-butyl alcohol (Figures I1 and I2). No ultraviolet/visible spectra were found in the literature. The boiling point and density of lot F112784 were consistent with literature values (*Merck Index*, 1983).

The purity of lot F112784 was determined by elemental analyses, Karl Fischer water analysis, and gas chromatography. Gas chromatography was performed with a flame ionization detector and a nitrogen carrier gas at a flow rate of 70 mL/minute. Two systems were used:

A) Porapak QS 80/100 glass mesh column with an oven temperature program of 50° C for 5 minutes, then to 250° C at 10° C per minute, and

B) 80/100 Carbopack C/0.1% SP-1000 glass column with an oven temperature program of 50° C for 5 minutes, then to 225° C at 10° C per minute.

For lot F112784, a neat sample and a sample solution containing 1% *t*-butyl alcohol by volume in methanol were analyzed with system A with an isothermal oven temperature of 200° C. A neat sample and a second sample solution containing 1% *t*-butyl alcohol by volume in methylene chloride were analyzed with system B with an isothermal oven temperature of 55° C. A test sample solution containing 0.5% *t*-butyl alcohol by volume in methylene chloride and a frozen reference sample were concomitantly analyzed with system B but with an isothermal column temperature of 50° C and with *n*-propyl alcohol as an internal standard.

Elemental analyses for carbon and hydrogen in lot F112784 were in agreement with the theoretical values for *t*-butyl alcohol; Karl Fischer water analysis indicated 0.026% ± 0.001% water. Gas chromatography with each system indicated one major peak and one impurity with a peak area greater than or equal to 0.1% relative to the major peak. The overall purity of lot F112784 was determined to be greater than 99%.

Accelerated stability studies were performed on lot F112784 by the analytical chemistry laboratory. Gas chromatography was performed with system B as described above for the purity analysis but with an isothermal column temperature of 50° C. Sample solutions contained 0.5% *t*-butyl alcohol by volume in methylene chloride; 0.5% *n*-propyl alcohol was added as an internal standard. Results indicated that *t*-butyl alcohol was stable as a bulk chemical when stored for 2 weeks protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored protected from light at room temperature in amber glass bottles with Teflon-lined lids. Stability was monitored during the 13-week and 2-year studies with gas chromatography. No degradation of the bulk chemical was detected.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared by mixing *t*-butyl alcohol with deionized water (Table I1). Formulations were stored in glass bottles at room temperature for up to 2 weeks.

Stability studies of the 0.5 mg/mL dose formulation were performed by the analytical chemistry laboratory. Gas chromatography with system A as previously described with an isothermal column temperature of 170° C and a carrier gas flow rate of 30 mL/min was used. The stability of the dose formulations was confirmed when stored in the dark for at least 3 weeks at room temperature and for at least 3 days at room temperature under normal room light.

Periodic analyses of the dose formulations of *t*-butyl alcohol were conducted at the study laboratory and analytical chemistry laboratory with gas chromatography. During the 13-week drinking water studies, the formulations were analyzed at the beginning, middle, and end of the studies (Table I2). During the 2-year studies, the formulations were analyzed approximately every 8 weeks (Table I3). All of the dose formulations analyzed were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I4).

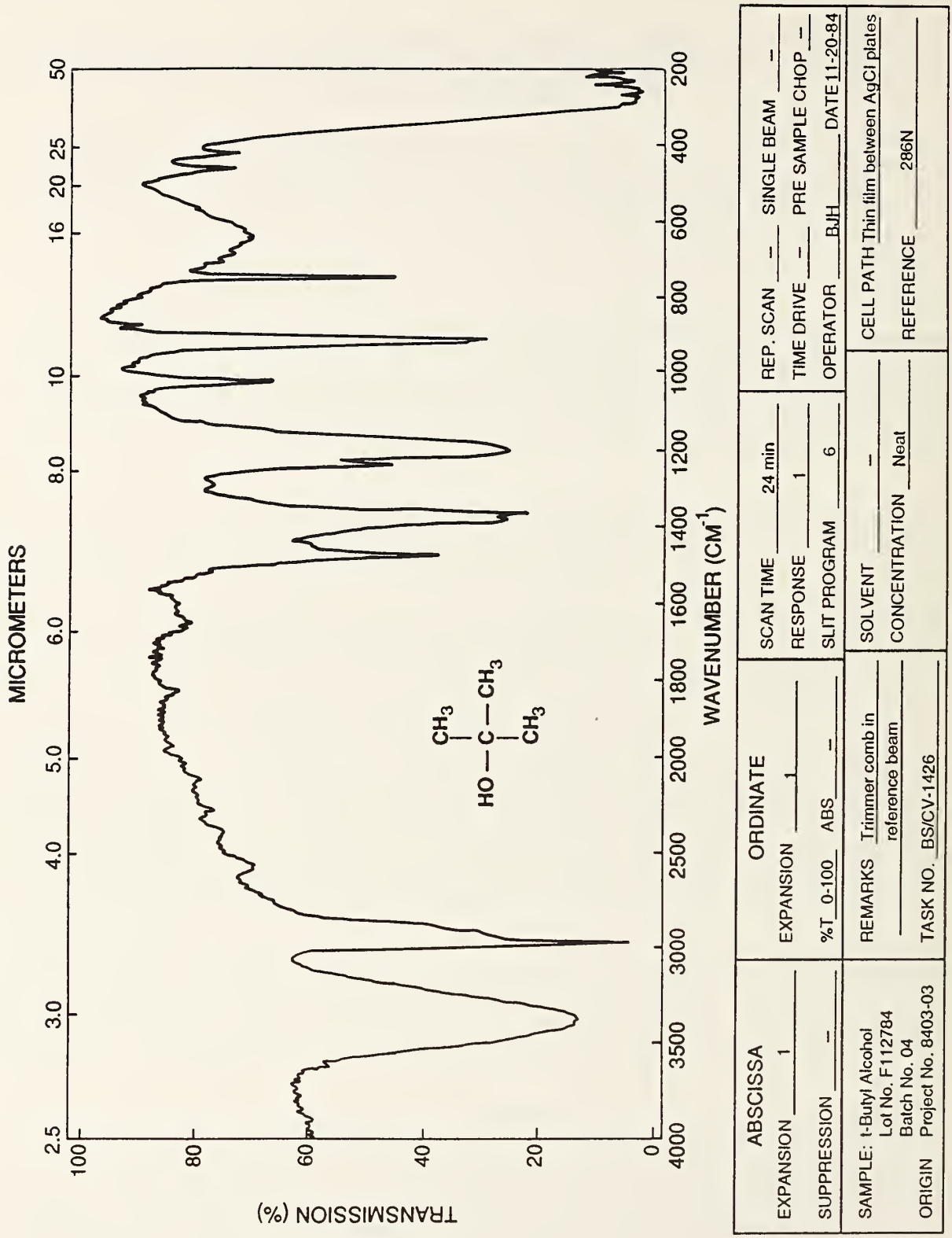


Figure I1
Infrared Absorption Spectrum of *t*-Butyl Alcohol

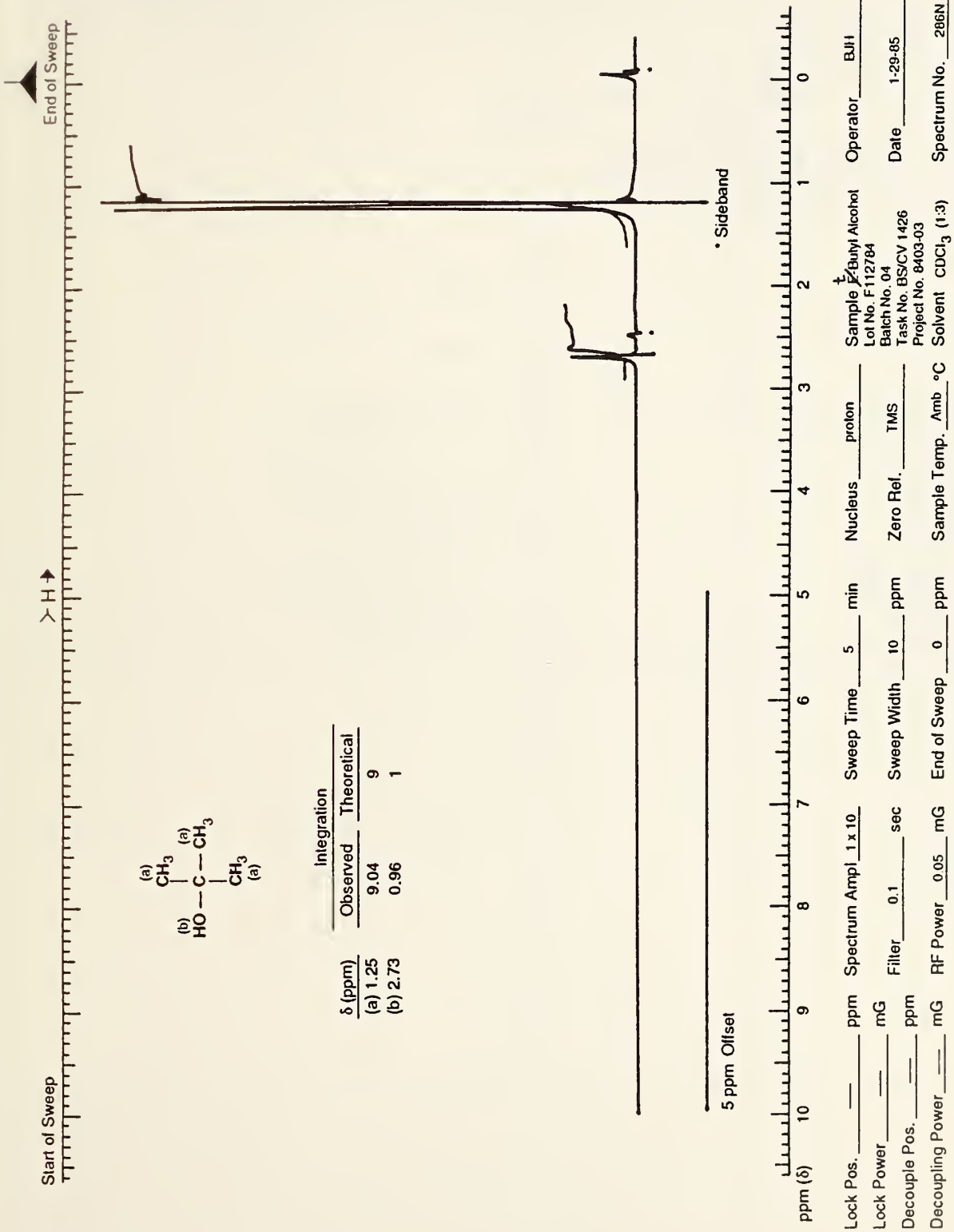


FIGURE I2
Nuclear Magnetic Resonance Spectrum of *t*-Butyl Alcohol

TABLE I1
Preparation and Storage of Dose Formulations in the Drinking Water Studies of *t*-Butyl Alcohol

13-Week Studies	2-Year Studies
Preparation	
t-Butyl alcohol was mixed with approximately one-half the required volume of deionized water, diluted to the specified volume with additional deionized water, and stirred for at least 5 minutes.	Same as 13-week studies
Chemical Lot Number	
F112784	F112784
Maximum Storage Time	
2 Weeks	2 Weeks
Storage Conditions	
Stored in amber glass bottles with Teflon-lined lids in the dark at room temperature	Same as 13-week studies
Study Laboratory	
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)
Referee Laboratory	
Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)

TABLE 12
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week Drinking Water Studies of *t*-Butyl Alcohol

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)[a]	% Difference from Target
26 November 1985	26 November 1985	2.50	2.52	+1
		5.00	5.04	+1
		10.0	10.1	+1
		20.0	20.2	+1
		40.0	39.9	0
	6 December 1985[b]	2.50	2.54	+2
		5.00	5.06	+1
		10.0	10.3	+3
		20.0	20.0	0
		40.0	39.9	0
9 January 1986	9–10 January 1986	2.50	2.56	+2
		5.00	5.11	+2
		10.0	10.2	+2
		20.0	20.0	0
		40.0	40.4	+1
	20 January 1986[b]	2.50	2.48	–1
		2.50	2.48	–1
		5.00	5.03	+1
		5.00	5.02	0
		10.0	9.92	–1
		10.0	9.92	–1
		20.0	19.8	–1
		20.0	19.2	–4
		40.0	39.2	–2
		40.0	39.1	–2
6 March 1986	6 March 1986	2.50	2.47	–1
		5.00	5.02	0
		10.0	9.95	–1
		20.0	20.2	+1
		40.0	40.6	+2
	17 March 1986[b]	2.50	2.42	–3
		5.00	4.92	–2
		10.0	9.76	–2
		20.0	19.7	–2
		40.0	39.2	–2

[a] Results of duplicate analyses
[b] Animal room samples

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of *t*-Butyl Alcohol

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)[a]	% Difference from Target
Rats				
6 November 1986	7 November 1986	1.25	1.28	+2
		1.25	1.26	+1
		2.50	2.52	+1
		5.00	5.06	+1
		5.00	5.05	+1
		10.0	10.2	+2
	14–15 November 1986[b]	1.25	1.24	–1
		2.50	2.53	+1
		5.00	4.91	–2
		10.0	10.4	+4
8 January 1987	8–9 January 1987	1.25	1.30	+4
		1.25	1.24	–1
		2.50	2.49	0
		5.00	4.99	0
		5.00	4.98	0
		10.0	9.94	–1
12 March 1987	12–13 March 1987	1.25	1.32	+6
		1.25	1.27	+2
		2.50	2.55	+2
		5.00	5.06	+1
		5.00	4.72	–6
		10.0	9.14	–9
7 May 1987	8–9 May 1987	1.25	1.28	+2
		1.25	1.26	+1
		2.50	2.52	+1
		5.00	5.08	+2
		5.00	5.10	+2
		10.0	10.3	+3
	18–19 May 1987[b]	1.25	1.26	+1
		2.50	2.51	0
		5.00	5.00	0
		10.0	10.1	+1
9 July 1987	9–10 July 1987	1.25	1.30	+4
		1.25	1.29	+3
		2.50	2.55	+2
		5.00	5.06	+1
		5.00	5.12	+2
		10.0	10.2	+2

TABLE 13
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of *t*-Butyl Alcohol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Rats (continued)				
3 September 1987	4–5 September 1987	1.25	1.30	+4
		1.25	1.31	+5
		2.50	2.51	0
		5.00	5.00	0
		5.00	5.04	+1
		10.0	9.98	0
12 November 1987	12–13 November 1987	1.25	1.22	−2
		1.25	1.23	−2
		2.50	2.54	+2
		5.00	4.98	0
		5.00	5.12	+2
		10.0	10.2	+2
	20–21 November 1987[b]	1.25	1.26	+1
		2.50	2.52	+1
		5.00	5.04	+1
		10.0	9.98	0
6 January 1988	8 and 11 January 1988	1.25	1.30	+4
		1.25	1.26	+1
		2.50	2.57	+3
		5.00	5.04	+1
		5.00	5.07	+1
		10.0	10.2	+2
18 February 1988	18–19 February 1988	1.25	1.28	+2
		1.25	1.24	−1
		2.50	2.50	0
		2.50	2.50	0
		5.00	5.01	0
		5.00	4.98	0
		10.0	10.1	+1
14 April 1988	15–16 April 1988	1.25	1.27	+2
		1.25	1.26	+1
		2.50	2.44	−2
		2.50	2.54	+2
		5.00	5.04	+1
		5.00	4.93	−1
		10.0	10.0	0
	22 and 27 April 1988[b]	1.25	1.23	−2
		2.50	2.76	+10
		5.00	5.08	+2
		10.0	10.0	0

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of *t*-Butyl Alcohol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Rats (continued)				
9 June 1988	9–10 June 1988	1.25	1.26	+1
		1.25	1.24	–1
		2.50	2.56	+2
		5.00	5.00	0
		5.00	5.02	0
		10.0	10.0	0
28 July 1988	28 July–1 August 1988	1.25	1.21	–3
		1.25	1.20	–4
		2.50	2.47	–1
		5.00	4.98	0
		5.00	5.06	+1
		10.0	10.2	+2
22 September 1988	22–23 September 1988	1.25	1.29	+3
		1.25	1.30	+4
		2.50	2.70	+8
		5.00	5.15	+3
		5.00	5.15	+3
		10.0	10.4	+4
27 October 1988	27–28 October 1988	1.25	1.26	+1
		2.50	2.48	–1
		5.00	4.97	–1
		10.0	10.2	+2
	3–4 November 1988[b]	1.25	1.26	+1
		2.50	2.50	0
		5.00	4.84	–3
		10.0	10.2	+2
Mice				
13 November 1986	14–15 November 1986	5.00	5.08	+2
		5.00	5.04	+1
		10.0	9.90	–1
		20.0	19.7	–2
		20.0	19.4	–3
	24 November 1986[b]	5.00	5.14	+3
		10.0	10.1	+1
		20.0	18.9	–6
8 January 1987	8–9 January 1987	5.00	4.99	0
		5.00	4.98	0
		10.0	9.94	–1
		20.0	20.2	+1
		20.0	19.7	–2

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of *t*-Butyl Alcohol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Mice (continued)				
12 March 1987	12–13 March 1987	5.00	5.06	+1
		5.00	4.72	–6
		10.0	9.14	–9
		20.0	20.4	+2
		20.0	20.1	+1
7 May 1987	8–9 May 1987	5.00	5.08	+2
		5.00	5.10	+2
		10.0	10.3	+3
		20.0	20.5	+3
		20.0	19.8	–1
	18–19 May 1987[b]	5.00	5.00	0
		10.0	10.1	+1
		20.0	19.6	–2
9 July 1987	9–10 July 1987	5.00	5.06	+1
		5.00	5.12	+2
		10.0	10.2	+2
		20.0	20.4	+2
		20.0	19.7	–2
3 September 1987	4–5 September 1987	5.00	5.00	0
		5.00	5.04	+1
		10.0	9.98	0
		20.0	19.7	–2
12 November 1987	12–13 November 1987	5.00	4.98	0
		5.00	5.12	+2
		10.0	10.2	+2
		20.0	20.0	0
	20–21 November 1987[b]	5.00	5.04	+1
		10.0	9.98	0
6 January 1988	8 and 11 January 1988	5.00	5.04	+1
		5.00	5.07	+1
		10.0	10.2	+2
		20.0	19.8	–1
18 February 1988	18–19 February 1988	5.00	5.01	0
		5.00	4.98	0
		10.0	10.1	+1
		20.0	19.9	–1

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of *t*-Butyl Alcohol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Mice (continued)				
14 April 1988	15–16 April 1988	5.00	5.04	+1
		5.00	4.93	–1
		10.0	10.0	0
		20.0	19.6	–2
	22 and 27 April 1988[b]	5.00	5.08	+2
		10.0	10.0	0
		20.0	19.9	–1
9 June 1988	9–10 June 1988	5.00	5.00	0
		5.00	5.02	0
		10.0	10.0	0
		20.0	19.8	–1
28 July 1988	28 July–1 August 1988	5.00	4.98	0
		5.00	5.06	+1
		10.0	10.2	+2
		20.0	19.7	–2
22 September 1988	22–23 September 1988	5.00	5.15	+3
		5.00	5.15	+3
		10.0	10.4	+4
		20.0	21.0	+5
27 October 1988	27–28 October 1988	5.00	4.97	–1
		10.0	10.2	+2
		20.0	20.0	0
	3–4 November 1988[b]	5.00	4.84	–3
		10.0	10.2	+2
		20.0	19.9	–1

[a] Results of duplicate analyses
[b] Animal room samples

TABLE 14
Results of Referee Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Drinking Water Studies of *t*-Butyl Alcohol

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL) Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies (Southern Research Institute)			
26 November 1985	2.50	2.52	2.49 ± 0.04
6 March 1986	10.0	9.95	9.94 ± 0.03
2-Year Studies (Southern Research Institute)			
Rats			
6 November 1986	2.50	2.52	2.50 ± 0.06
14 April 1988	5.00	5.04	5.00 ± 0.07
7 May 1987	10.0	10.3	10.0 ± 0.3
27 October 1988	1.25	1.26	1.26 ± 0.02
Mice			
12 November 1987	20.0	20.0	18.0 ± 0.4
14 April 1988	5.00	5.04	5.00 ± 0.07
7 May 1987	10.0	10.3	10.0 ± 0.3

[a] Results of duplicate analyses.
[b] Results of triplicate analyses (mean ± standard error)

APPENDIX J
WATER AND COMPOUND CONSUMPTION IN THE 2-YEAR DRINKING WATER STUDIES

TABLE J1 Water and Compound Consumption by Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 300

TABLE J2 Water and Compound Consumption by Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 301

TABLE J3 Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 302

TABLE J4 Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol 303

TABLE J1
Water and Compound Consumption by Male Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

	0 mg/mL		1.25 mg/mL			2.5 mg/mL			5 mg/mL		
Week	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)[b]	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	22.4	175	21.8	175	156	22.5	174	322	22.0	173	638
4	22.3	237	24.1	234	128	25.7	237	271	23.8	230	518
6	23.0	275	24.1	272	111	26.1	276	237	23.6	269	439
8	22.7	306	23.9	300	100	27.2	302	225	23.2	296	392
10	23.6	329	24.9	320	97	27.7	326	212	25.4	320	397
12	23.2	345	25.6	335	96	27.8	341	203	24.6	332	371
13	22.3	349	24.1	340	89	28.3	346	204	25.6	337	380
17	21.2	374	23.2	370	78	24.7	371	167	23.3	362	322
21	21.1	384	21.7	374	73	24.1	377	159	23.3	365	319
25	21.0	409	20.6	395	65	23.5	402	146	23.2	388	300
29	21.5	424	21.0	411	64	23.4	419	140	23.1	401	288
33	20.0	439	21.7	425	64	23.3	432	134	23.3	416	280
37	21.2	441	22.1	427	65	23.3	434	134	24.2	416	292
41	20.2	451	20.5	439	58	22.3	448	125	23.0	432	267
45	20.7	459	21.1	448	59	23.4	454	129	20.8	437	238
49	22.0	463	22.4	451	62	24.7	456	136	25.2	440	287
53	21.5	468	23.1	455	64	25.0	458	137	25.6	438	293
57	22.8	477	23.8	464	64	25.8	466	138	26.7	447	299
61	24.5	480	25.5	463	69	26.4	462	143	27.6	438	315
65	27.2	486	29.9	467	80	31.7	467	170	30.4	436	348
69	28.2	481	30.7	464	83	36.0	458	197	39.8	430	463
73	30.7	484	32.1	464	86	37.9	454	209	45.3	422	538
77	32.0	479	34.4	464	93	40.6	451	225	46.2	424	545
81	33.2	469	34.8	447	97	39.7	419	237	45.0	377	597
85	31.9	468	37.4	459	102	43.8	433	253	42.8	388	551
89	36.8	468	39.0	440	111	45.9	412	279	47.7	400	596
93	36.6	481	45.2	433	131	56.2	430	327	51.5	395	652
97	38.1	462	42.9	417	129	50.2	406	310	53.2	385	690
101	36.4	454	38.0	387	123	46.0	374	307	56.6	344	823
Mean for weeks											
1-13	22.8	288	24.1	282	111	26.5	286	239	24.0	280	448
14-52	21.0	427	21.6	415	65	23.6	421	141	23.3	406	288
53-101	30.8	474	33.6	448	95	38.9	438	225	41.4	410	516

[a] Grams of water consumed per animal per day.
[b] Milligrams of *t*-butyl alcohol consumed per kilogram body weight per day

TABLE J2
Water and Compound Consumption by Female Rats in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

	0 mg/mL		2.5 mg/mL			5 mg/mL			10 mg/mL		
Week	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)[b]	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	19.8	120	19.5	121	401	19.2	119	803	16.4	118	1,393
4	18.8	146	20.0	147	341	17.5	146	597	14.6	148	987
6	17.2	166	18.3	165	276	15.5	164	472	12.5	166	754
8	18.4	178	18.1	177	256	14.5	176	410	13.2	177	750
10	17.1	188	17.3	185	234	15.5	185	418	13.5	186	729
12	17.8	195	17.9	193	232	14.0	193	362	13.6	193	702
14	16.4	204	17.0	200	213	14.5	200	361	12.5	199	628
17	16.9	209	16.4	207	197	13.8	206	335	12.5	205	610
21	16.6	215	15.7	214	184	14.3	207	344	12.4	207	596
25	16.8	225	15.8	221	179	14.4	219	329	12.7	216	588
29	16.0	232	16.1	229	176	14.0	226	309	12.8	220	581
33	15.7	240	15.6	237	165	13.9	235	295	13.2	229	576
37	16.7	244	15.7	238	165	15.2	238	320	14.0	233	601
41	16.7	253	15.4	250	154	14.8	248	298	13.2	239	554
45	16.4	262	15.9	257	155	14.3	255	282	13.7	244	563
49	16.7	271	16.3	267	153	15.4	263	293	14.3	252	570
53	16.3	278	16.1	271	149	15.4	271	284	14.4	256	562
57	17.5	288	16.2	282	144	15.4	281	273	14.9	264	562
62	19.3	300	18.4	291	158	16.9	291	290	16.0	272	587
65	19.1	304	19.5	296	165	18.1	297	304	16.8	276	610
69	19.8	310	19.5	305	160	18.0	303	297	17.0	280	607
73	20.1	313	18.2	312	146	18.5	308	300	16.8	285	591
77	19.6	318	19.2	315	152	18.5	311	297	18.3	287	637
81	18.1	326	18.4	323	142	17.4	315	276	18.4	289	637
85	19.9	327	18.4	326	141	16.8	322	260	18.7	288	648
89	19.7	335	18.8	330	142	18.4	326	283	18.1	294	616
93	21.1	337	19.0	336	142	18.9	321	294	19.6	293	668
97	22.4	336	19.9	333	150	21.1	326	323	19.6	273	717
101	22.3	331	20.6	324	159	19.2	316	304	20.9	261	802
Mean for weeks											
1-13	18.2	165	18.5	165	290	16.0	164	511	14.0	165	886
14-52	16.5	236	16.0	232	174	14.5	230	317	13.1	224	587
53-101	19.6	316	18.6	311	150	17.9	307	291	17.6	278	634

[a] Grams of water consumed per animal per day.
[b] Milligrams of *t*-butyl alcohol consumed per kilogram body weight per day

TABLE J3
Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

	0 mg/mL		5 mg/mL			10 mg/mL			20 mg/mL		
Week	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)[b]	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	5.3	27.5	5.6	27.4	1,023	4.9	27.3	1,805	4.5	27.0	3,315
4	5.4	31.0	5.3	31.2	841	5.0	30.7	1,633	5.1	30.1	3,418
6	5.1	33.7	4.9	33.2	734	4.8	33.2	1,459	4.9	32.2	3,018
8	5.1	36.7	5.1	36.6	697	4.9	35.6	1,366	4.8	34.4	2,797
10	5.1	38.9	5.0	38.5	649	4.8	37.9	1,264	5.1	36.3	2,837
12	4.6	40.7	5.1	39.9	637	4.6	39.8	1,145	4.9	37.7	2,622
13	4.5	42.0	4.4	41.9	525	4.2	41.0	1,030	4.4	38.5	2,261
17	4.4	46.2	4.6	45.5	508	4.5	44.6	1,016	4.5	41.7	2,143
21	4.3	47.0	4.6	46.2	500	4.3	46.7	922	4.2	42.3	1,980
25	4.7	49.2	4.9	48.9	499	4.5	48.3	928	4.3	45.6	1,896
29	4.9	50.7	4.7	50.2	468	4.4	48.9	907	4.5	46.9	1,938
33	4.8	50.9	4.7	50.7	460	4.5	50.0	903	4.6	47.9	1,903
37	4.7	51.0	4.7	50.1	473	4.4	49.6	885	4.3	47.4	1,806
41	4.8	51.9	4.6	51.2	446	4.4	50.8	874	4.1	48.8	1,693
45	4.9	52.3	4.9	51.2	476	4.8	51.3	926	4.4	49.1	1,789
49	4.9	52.0	4.7	50.7	467	4.2	50.8	833	4.1	49.0	1,667
53	5.3	52.4	5.1	51.3	494	4.8	51.5	940	4.4	49.1	1,804
57	5.3	52.5	5.2	51.3	511	5.2	51.2	1,022	4.7	49.9	1,897
61	5.8	52.9	5.7	51.6	549	5.3	51.9	1,014	5.0	50.3	1,974
65	5.3	52.2	5.0	51.4	489	4.9	50.6	967	4.3	49.5	1,723
69	5.6	51.9	5.4	52.0	522	5.1	51.1	992	4.8	48.9	1,948
73	5.6	52.7	5.5	51.9	530	5.4	50.5	1,061	4.8	50.2	1,920
77	5.9	52.9	5.6	52.3	533	5.7	50.4	1,136	5.2	49.7	2,090
81	5.8	53.3	5.4	52.6	510	5.3	51.2	1,027	5.3	50.1	2,108
85	5.9	52.1	5.6	50.8	549	5.2	49.6	1,039	5.0	48.3	2,076
89	5.6	51.1	5.2	50.9	508	4.7	49.7	938	4.6	49.1	1,863
93	5.6	50.2	5.2	51.1	510	4.8	48.8	986	4.5	49.5	1,828
97	5.8	48.6	5.8	48.8	595	5.6	47.5	1,173	5.6	46.5	2,410
101	6.0	47.3	5.9	47.7	621	5.8	46.5	1,247	5.6	46.6	2,410
Mean for weeks											
1-13	5.0	35.8	5.0	35.5	729	4.7	35.1	1,386	4.8	33.7	2,896
14-52	4.7	50.1	4.7	49.4	478	4.5	49.0	910	4.3	46.5	1,868
53-101	5.7	51.5	5.4	51.1	532	5.2	50.0	1,042	4.9	49.1	2,004

[a] Grams of water consumed per animal per day.
[b] Estimated milligrams of *t*-butyl alcohol consumed per kilogram body weight per day

TABLE J4
Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of *t*-Butyl Alcohol

	0 mg/mL		5 mg/mL			10 mg/mL			20 mg/mL		
Week	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)[b]	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	5.3	20.9	5.0	20.4	1,214	4.5	20.6	2,164	3.9	20.0	3,851
4	5.3	24.1	4.9	23.7	1,029	4.8	23.7	2,023	4.7	23.3	4,058
5	5.3	25.2	4.9	24.6	998	4.8	24.8	1,953	4.6	24.0	3,862
7	5.3	27.5	4.9	27.1	906	4.8	27.4	1,768	4.6	26.3	3,524
8	5.4	28.7	5.1	28.2	901	4.7	28.3	1,669	4.6	27.1	3,389
10	5.9	30.5	5.4	29.8	898	5.1	29.9	1,696	4.6	28.6	3,247
12	5.2	33.0	5.1	31.8	794	4.6	32.0	1,445	4.6	30.1	3,069
13	4.8	34.4	4.6	33.2	685	4.4	32.9	1,325	4.5	30.9	2,901
17	4.6	39.4	4.7	38.1	615	4.6	37.7	1,222	4.6	35.1	2,601
21	4.4	43.5	4.3	42.0	516	4.5	41.0	1,088	4.3	37.7	2,300
25	4.4	45.7	4.5	43.8	516	4.7	42.5	1,113	4.6	39.5	2,318
29	4.0	48.1	4.3	46.4	460	4.3	44.9	957	4.3	41.8	2,053
30	4.2	48.5	4.3	47.1	457	4.5	45.7	989	4.5	42.3	2,123
33	4.2	49.8	4.2	48.1	435	4.3	46.5	932	4.5	43.3	2,061
37	4.1	50.3	4.1	48.7	419	4.1	47.5	862	4.1	43.7	1,889
41	4.1	52.3	4.1	51.1	400	4.0	49.7	813	4.0	45.9	1,734
45	4.2	54.0	4.5	52.7	425	4.2	51.0	826	4.2	47.3	1,784
49	4.0	53.7	4.0	51.9	385	3.8	50.6	747	3.6	46.3	1,563
53	4.5	55.3	4.3	54.0	398	4.3	52.0	835	4.1	47.9	1,698
57	4.2	56.5	4.1	54.9	375	4.2	53.0	799	4.3	48.6	1,754
61	5.1	56.6	5.4	54.3	502	5.0	52.7	954	4.8	48.9	1,947
65	4.4	58.2	4.4	56.0	389	4.1	54.5	752	3.7	50.4	1,458
69	4.6	58.5	4.9	56.0	434	4.5	54.6	816	4.1	49.8	1,635
73	4.7	58.8	4.7	57.1	408	4.4	55.6	791	4.3	50.8	1,698
77	5.0	59.5	5.2	57.0	455	4.9	55.9	879	4.6	51.5	1,802
81	4.8	60.5	4.5	58.1	390	4.4	56.7	780	4.1	52.1	1,582
85	4.9	60.2	4.6	58.9	389	4.6	55.2	825	4.4	51.6	1,717
89	5.0	58.7	4.9	57.1	429	4.5	54.7	819	4.2	50.4	1,669
93	5.0	57.3	5.0	56.3	447	4.6	54.7	838	4.6	49.4	1,852
97	5.7	54.9	5.3	53.5	491	5.3	51.9	1,025	4.9	47.5	2,065
101	5.7	53.6	6.1	52.4	584	5.9	52.1	1,125	5.5	47.2	2,338
Mean for weeks											
1-13	5.3	28.0	5.0	27.4	928	4.7	27.5	1,755	4.5	26.3	3,488
14-52	4.2	48.5	4.3	47.0	463	4.3	45.7	955	4.3	42.3	2,043
53-101	4.9	57.6	4.9	55.8	438	4.7	54.1	865	4.4	49.7	1,786

[a] Grams of water consumed per animal per day.
[b] Estimated milligrams of *t*-butyl alcohol consumed per kilogram body weight per day

APPENDIX K
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

TABLE K1 Ingredients of NIH-07 Rat and Mouse Ration 306
TABLE K2 Vitamins and Minerals in NIH-07 Rat and Mouse Ration 306
TABLE K3 Nutrient Composition of NIH-07 Rat and Mouse Ration 307
TABLE K4 Contaminant Levels in NIH-07 Rat and Mouse Ration 308

TABLE K1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE K2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.60 ± 0.72	21.70 – 24.00	27
Crude Fat (% by weight)	5.48 ± 0.33	4.90 – 6.00	27
Crude Fiber (% by weight)	3.57 ± 0.26	3.20 – 4.20	27
Ash (% by weight)	6.81 ± 0.25	7.30 – 6.26	27
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 – 1.390	10
Cystine	0.306 ± 0.075	0.181 – 0.400	10
Glycine	1.160 ± 0.050	1.060 – 1.220	10
Histidine	0.580 ± 0.024	0.531 – 0.608	10
Isoleucine	0.917 ± 0.034	0.867 – 0.965	10
Leucine	1.972 ± 0.052	1.850 – 2.040	10
Lysine	1.273 ± 0.051	1.200 – 1.370	10
Methionine	0.437 ± 0.115	0.306 – 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 – 1.110	10
Threonine	0.896 ± 0.055	0.824 – 0.985	10
Tryptophan	0.223 ± 0.160	0.107 – 0.671	10
Tyrosine	0.677 ± 0.105	0.564 – 0.794	10
Valine	1.089 ± 0.057	0.962 – 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 – 2.570	9
Linolenic	0.277 ± 0.036	0.210 – 0.320	9
Vitamins			
Vitamin A (IU/kg)	6,589 ± 1,403	4,430 – 10,560	27
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 – 48.9	9
Thiamine (ppm)	19.30 ± 2.67	14.0 – 26.0	27
Riboflavin (ppm)	7.92 ± 0.93	6.10 – 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 – 150.0	9
Pantothenic Acid (ppm)	30.30 ± 3.60	23.0 – 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 – 14.0	10
Folic Acid (ppm)	2.51 ± 0.64	1.80 – 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 – 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 – 65.0	10
Choline (ppm)	3,068 ± 314	2,400 – 3,430	9
Minerals			
Calcium (%)	1.27 ± 0.13	1.00 – 1.54	27
Phosphorus (%)	0.94 ± 0.05	0.80 – 1.00	27
Potassium (%)	0.887 ± 0.067	0.772 – 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 – 0.635	8
Sodium (%)	0.315 ± 0.344	0.258 – 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 – 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 – 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 – 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 – 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 – 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 – 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 – 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 – 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 – 1.150	6

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.25 ± 0.19	0.05 – 0.80	27
Cadmium (ppm)[b]	<0.10		27
Lead (ppm)	0.31 ± 0.25	0.05 – 1.00	27
Mercury (ppm)	<0.05		27
Selenium (ppm)	0.35 ± 0.10	0.16 – 0.63	27
Aflatoxins (ppb)	<5.0		27
Nitrate nitrogen (ppm)[c]	21.96 ± 9.42	9.90 – 41.0	27
Nitrite nitrogen (ppm)[c]	0.23 ± 0.19	<0.10 – 0.90	27
BHA (ppm)[d]	1.93 ± 0.46	<0.10 – 3.00	27
BHT (ppm)[d]	1.07 ± 0.47	<0.10 – 3.00	27
Aerobic plate count (CFU/g)[e]	118,562 ± 189,115	4,770 – 940,000	27
Coliform (MPN/g)[f,g]	50.52 ± 211.64	<3.00 – 1,100	27
Coliform (MPN/g)[h]	10.15 ± 28.83	<3.00 – 150	26
E. coli (MPN/g)[i]	<3.00		27
Total Nitrosoamines (ppb)[j]	10.67 ± 4.67	3.60 – 20.00	27
N-Nitrosodimethylamine (ppb)[j]	8.42 ± 4.18	2.60 – 19.00	27
N-Nitrosopyrrolidine (ppb)[j]	2.18 ± 1.45	0.90 – 5.40	27
Pesticides (ppm)			
α-BHC[k]	<0.01		27
ß-BHC	<0.02		27
γ-BHC	<0.01		27
δ-BHC	<0.01		27
Heptachlor	<0.01		27
Aldrin	<0.01		27
Heptachlor epoxide	<0.01		27
DDE	<0.01		27
DDD	<0.01		27
DDT	<0.01		27
HCB	<0.01		27
Mirex	<0.01		27
Methoxychlor	<0.05		27
Dieldrin	<0.01		27
Endrin	<0.01		27
Telodrin	<0.01		27
Chlordane	<0.05		27
Toxaphene	<0.1		27
Estimated PCBs	<0.2		27
Ronnel	<0.01		27
Ethion	<0.02		27
Trithion	<0.05		27
Diazinon	<0.1		27
Methyl parathion	<0.02		27
Ethyl parathion	<0.02		27
Malathion	0.17 ± 0.16	0.05 – 0.60	27
Endosulfan I	<0.01		27
Endosulfan II	<0.01		27
Endosulfan sulfate	<0.03		27

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] One lot, milled June 3, 1987, contained 0.20 ppm. All other lots were measured at less than or equal to the detection limit.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] CFU=colony forming units
[f] MPN=most probable number
[g] Mean, range, and standard deviation include one unusually large value of 1,110 MPN/g from the lot milled July 5, 1988.
[h] Mean, range, and standard deviation exclude the value given in footnote [g].
[i] One lot, milled April 4, 1988, contained 4.0 MPN/g.
[j] All values were corrected for percent recovery.
[k] BHC is hexachlorocyclohexane or benzene hexachloride.

APPENDIX L
SENTINEL ANIMAL PROGRAM

Methods 312

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are all subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from as many as 10 control and 10 other randomly selected male and female rats and mice during the 13-week and 2-year studies. Blood from each animal was collected, allowed to clot, and the serum separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method of Analysis	Time of Analysis
RATS	
13-Week Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
M. arthritidis	24 months
M. pulmonis	24 months
PVM	6, 12, 18, and 24 months
RCV/SDA	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
Hemagglutination Inhibition	
H-1	6, 12, 18, and 24 months
KRV	6, 12, 18, and 24 months

MICE

13-Week Study

ELISA

Ectromelia virus	Quarantine and study termination
GDVII (mouse encephalomyelitis virus)	Quarantine and study termination
LCM (lymphocytic choriomeningitis virus)	Quarantine and study termination
MVM (minute virus of mice)	Quarantine and study termination
Mouse adenoma virus	Quarantine and study termination
MHV (mouse hepatitis virus)	Quarantine and study termination
PVM	Quarantine and study termination
Reovirus 3	Quarantine and study termination
Sendai	Quarantine and study termination

2-Year Study

ELISA

Ectromelia virus	6, 12, 18, and 24 months
GDVII	6, 12, 18, and 24 months
LCM	6, 12, and 18 months
MVM	6, 12, 18, and 24 months
Mouse adenoma virus	6, 12, 18, and 24 months
MHV	6, 12, and 24 months
M. arthritidis	24 months
M. pulmonis	24 months
PVM	6, 12, 18, and 24 months
Reovirus 3	6, 12, and 24 months
Sendai	6, 12, 18, and 24 months

Hemagglutination Inhibition

K (papovavirus)	6, 12, 18, and 24 months
Polyoma virus	6, 12, 18, and 24 months

Immunofluorescence Assay

EDIM (epizootic diarrhea of infant mice)	6, 12, 18, and 24 months
LCM	24 months
MHV	18 months
Reovirus 3	18 months

All test results were negative.

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PRINTED AS OF MAY 1995

TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4′-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl)phosphonium Sulfate & Tetrakis(hydroxymethyl)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5
311	Tetrachloroethylene (Inhalatic
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochlorid
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonat
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

LIBRARY
NIH
Amazing Research.
Amazing Help.
http://nihlibrary.nih.gov
10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

☆U.S. GOVERNMENT PRINTING OFFICE : 1995 398-120 QL 3

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF MAY 1995 (CONT.)

TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	α-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
384	1,2,3-Trichloropropane
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
398	Polybrominated Biphenyls
399	Titanocene Dichloride
400	2,3-Dibromo-1-propanol
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
404	5,5-Diphenylhydantoin
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
408	Mercuric Chloride
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-stilbenedisulfonic Acid
413	Ethylene Glycol
414	Pentachloroanisole
415	Polysorbate 80
416	*o*-Nitroanisole
417	*p*-Nitrophenol
418	*p*-Nitroaniline
419	HC Yellow 4
420	Triamterene
421	Talc
422	Coumarin
423	Dihydrocoumarin
424	*o*-Benzyl-*p*-chlorophenol
425	Promethazine Hydrochloride
426	Corn Oil, Safflower Oil, and Tricaprylin
427	Turmeric Oleoresin
428	Manganese (II) Sulfate Monohydrate
430	C.I. Direct Blue 218
431	Benzyl Acetate
432	Barium Chloride Dihydrate
433	Tricresyl Phosphate
434	1,3-Butadiene
435	4,4′-Thiobis(6-*t*-butyl-*m*-cresol)
437	Hexachlorocyclopentadiene
440	Ozone and Ozone/NNK
442	*p*-Nitrobenzoic Acid
443	Oxazepam

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709.

NIH LIBRARY
3 1496 00681 5388

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD A0-01
Research Triangle Park, NC 27709

SPECIAL FOURTH-CLASS RATE
POSTAGE AND FEES PAID
DHHS/NIH
Permit No. G-763

Official Business
Penalty for Private Use - $300

HEALTH LIBRARY
NATIONAL INSTITUTES OF HEALTH
MONOGRAPHS PROCESSING UNIT
BUILDING 10/ROOM 1L13
BETHESDA, MD
20892

NIH Publication No. 95-3167
May 1995